UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

In Re: TAXOTERE (DOCETAXEL) PRODUCTS LIABILITY LITIGATION

MDL NO. 2740

SECTION "H" (5)

THIS DOCUMENT RELATES TO ALL CASES

***EX PARTE* MOTION FOR LEAVE TO FILE PLAINTIFFS' REPLY IN SUPPORT OF PLAINTIFFS' MOTION FOR LEAVE TO FILE PLAINTIFFS' THIRD AMENDED MASTER LONG-FORM COMPLAINT**

NOW INTO COURT comes Plaintiffs, through the Plaintiffs' Steering Committee ("PSC"), who respectfully requests leave of Court to file the attached Plaintiffs' Reply in Support of Plaintiffs' Motion for Leave to File Plaintiffs' Third Amended Master Long-Form Complaint. The attached reply memorandum will assist the Court in evaluating the issues.

WHEREFORE, Plaintiffs pray that this Honorable Court grant this motion for leave to file the attached Plaintiffs' Motion for Leave to File Plaintiffs' Third Amended Master Long-Form Complaint.

Dated: December 3, 2019

Respectfully submitted,

/s/ Christopher L. Coffin
Christopher L. Coffin (#27902)
PENDLEY, BAUDIN & COFFIN, L.L.P.
1100 Poydras Street, Suite 2505
New Orleans, Louisiana 70163
Phone: (504) 355-0086
Fax: (504) 355-0089
ccoffin@pbclawfirm.com

Plaintiffs' Co-Lead Counsel

/s/ Karen B. Menzies
Karen Barth Menzies (CA Bar #180234)
Andre Mura (CA Bar # 298541)
GIBBS LAW GROUP LLP
6701 Center Drive West, Suite 1400
Los Angeles, California 90045
Telephone: 510-350-9700
Facsimile: 510-350-9701
kbm@classlawgroup.com

Plaintiffs' Co-Lead Counsel

/s/ M. Palmer Lambert
M. Palmer Lambert (#33228)
GAINSBURGH BENJAMIN DAVID
MEUNIER & WARSHAUER, LLC
2800 Energy Centre, 1100 Poydras Street
New Orleans, LA 70163-2800
Phone: 504-522-2304
Fax: 504-528-9973
plambert@gainsben.com

Plaintiffs' Co-Liaison Counsel

/s/ Dawn M. Barrios
Dawn M. Barrios (#2821)
BARRIOS, KINGSDORF & CASTEIX, LLP
701 Poydras Street, Suite 3650
New Orleans, LA 70139
Phone: 504-524-3300
Fax: 504-524-3313
barrios@bkc-law.com

Plaintiffs' Co-Liaison Counsel

PLAINTIFFS' STEERING COMMITTEE

Anne Andrews
Andrews Thornton Higgins Razmara, LLP
2 Corporate Park, Suite 110
Irvine, CA 92606
Phone: (800) 664-1734
aa@andrewsthornton.com

Daniel P. Markoff
Atkins & Markoff Law Firm
9211 Lake Hefner Parkway, Suite 104
Oklahoma City, OK 73120
Phone: (405) 607-8757
Fax: (405) 607-8749
dmarkoff@atkinsandmarkoff.com

J. Kyle Bachus
Bachus & Schanker, LLC
1899 Wynkoop Street, Suite 700
Denver, CO 80202
Phone: (303) 893-9800
Fax: (303) 893-9900
kyle.bachus@coloradolaw.net

Abby E. McClellan
Stueve Siegel Hanson LLP
460 Nichols Road, Suite 200
Kansas City, MO 64112
Phone: (816) 714-7100
Fax: (816) 714-7101
mcclellan@stuevesiegel.com

Lawrence J. Centola, III
Martzell, Bickford & Centola
338 Lafayette Street
New Orleans, LA 70130
Phone: (504) 581-9065
Fax: (504) 581-7635
lcentola@mbfirm.com

Karen Barth Menzies
Gibbs Law Group LLP
6701 Center Drive West, Suite 1400
Los Angeles, California 90045
Phone: 510-350-9700
Fax: 510-350-9701
kbm@classlawgroup.com

Christopher L. Coffin
Pendley, Baudin & Coffin, L.L.P.
1100 Poydras Street, Suite 2505
New Orleans, Louisiana 70163
Phone: (504) 355-0086
Fax: (504) 355-0089
ccoffin@pbclawfirm.com

David F. Miceli
David F. Miceli, LLC
P.O. Box 2519
Carrollton, GA 30112
Phone: (404) 915-8886
dmiceli@miceli-law.com

Alexander G. Dwyer
Kirkendall Dwyer LLP
440 Louisiana, Suite 1901
Houston, TX 77002
Phone: (713) 522-3529
Fax: (713) 495-2331
adwyer@kirkendalldwyer.com

Rand P. Nolen
Fleming, Nolen & Jez, L.L.P.
2800 Post Oak Blvd., Suite 4000
Houston, TX 77056
Phone: (713) 621-7944
Fax: (713) 621-9638
rand_nolen@fleming-law.com

Emily C. Jeffcott
Morgan & Morgan
700 S. Palafox Street, Suite 95
Pensacola, Florida 32505
Phone: (850) 316-9074
Fax: (850) 316-9079
ejeffcott@forthepeople.com

Hunter J. Shkolnik
Napoli Shkolnik PLLC
360 Lexington Avenue, 11th Floor
New York, NY 10017
Phone: (212) 397-1000
hunter@napolilaw.com

Andrew Lemmon
Lemmon Law Firm, LLC
P.O. Box 904
15058 River Road
Hahnville, LA 70057
Phone: (985) 783-6789
Fax: (985) 783-1333
andrew@lemmonlawfirm.com

Genevieve Zimmerman
Meshbesher & Spence Ltd.
1616 Park Avenue South
Minneapolis, MN 55404
Phone: (612) 339-9121
Fax: (612) 339-9188
gzimmerman@meshbesher.com

CERTIFICATE OF SERVICE

I hereby certify that on December 3, 2019, I electronically filed the foregoing with the Clerk of Court by using the CM/ECF system which will send a notice of electronic filing to all counsel of record who are CM/ECF participants.

/s/ M. Palmer Lambert
M. PALMER LAMBERT

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

In Re: TAXOTERE (DOCETAXEL) PRODUCTS LIABILITY LITIGATION

MDL NO. 2740

SECTION "H" (5)

THIS DOCUMENT RELATES TO:
ALL CASES

[PROPOSED] ORDER

Considering the foregoing *Ex Parte* Motion for Leave to File Plaintiffs' Reply in Support of Plaintiffs' Motion for Leave to File Plaintiffs' Third Amended Master Long-Form Complaint,

IT IS ORDERED that said Motion is GRANTED;

IT IS FURTHER ORDERED that the Clerk of Court shall file Plaintiffs' Reply in Support of Plaintiffs' Motion for Leave to File Plaintiffs' Third Amended Master Long-Form Complaint into the record in this matter.

New Orleans, Louisiana, this ___ of December, 2019.

_____
HON. JANE TRICHE MILAZZO
UNITED STATES DISTRICT JUDGE

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

In Re: TAXOTERE (DOCETAXEL) PRODUCTS LIABILITY LITIGATION

MDL NO. 2740

SECTION "H" (5)

THIS DOCUMENT RELATES TO ALL CASES

PLAINTIFFS' REPLY IN SUPPORT OF PLAINTIFFS' MOTION FOR LEAVE TO FILE PLAINTIFFS' THIRD AMENDED MASTER LONG-FORM COMPLAINT

Plaintiffs are not adding new theories or claims for relief to their proposed Third Amended Master Complaint. Rather, Plaintiffs seek to clarify certain allegations regarding permanent hair loss that Defendants have repeatedly misconstrued, claiming that Plaintiffs have defined permanent hair loss as occurring "no later than" six months following chemotherapy. This is simply inaccurate, and Plaintiffs seek to correct this misunderstanding by adding facts regarding (1) the definitions used for permanent hair-loss and (2) Sanofi's knowledge of permanent hair-loss among women using Taxotere but repeated and deliberate failure to warn women about this in the United States.

First, Plaintiffs' proposed amendments clarify the definition of permanent hair loss to align with medical literature and sworn statements from Sanofi's employees. Defendants do not dispute any of the facts contained in Plaintiffs' proposed amendment on this issue. They nonetheless object, claiming that this litigation has been operating under a single definition of permanent hair loss that Plaintiffs "were injured no later than six months after finishing chemotherapy." This is simply not true. Neither Plaintiffs, Plaintiffs' experts, nor the medical community at large have accepted such a strict definition for chemotherapy induced permanent hair loss. Indeed, outside of the courtroom, Sanofi itself has not adopted this six-month definition. Rather, Sanofi has

internally defined "persistent hair loss" as occurring at 12 months, 24 months, and 48 months post-chemotherapy.[1] Defendants ignore this, instead claiming that additional discovery will be necessary to address the prejudice inflicted by these "new definitions" of permanent hair-loss. But these definitions are not new. In fact, it was through discovery that Plaintiffs learned that Sanofi defined "persistent hair loss" using the more conservative 12 months, 24 months, and 48 months. Moreover, Plaintiffs' experts have not used the definition that permanent hair loss manifests itself "no later than six months following chemotherapy" as suggested by Defendants. For example, Dr. Kessler's original Expert Report from October of 2018 includes an entire section devoted to the various definitions of permanent hair loss, including those used internally by Sanofi[2]—a point he has reiterated at trial and in his most recent deposition taken just last week.[3] Additionally, Plaintiffs' experts Dr. Tosti, Dr. Feigal, and Dr. Plunkett have all stated that permanent hair loss requires "at least" or "more than" six months of no hair regrowth,[4] pointing to medical literature that defines permanent hair loss ranging from six months to 36 months. This is far different than the definition put forth by Defendants that permanent hair loss manifests itself "no later than" six months no discovery has never been limited to such a definition. Accordingly, Plaintiffs' proposed amendment serves to align Plaintiffs' Master Complaint with the undisputed facts case and clarify that there is no definitive definition of permanent hair loss as purported by Defendants.

Second, Plaintiffs' proposed amendments add allegations regarding Sanofi's knowledge that its U.S. label failed to warn women about the risk of permanent hari loss and Sanofi's efforts to remove information about permanent hair loss from its Facebook Page. Defendants objects to

[1] Ex. A, Sanofi_04353204 at 18; Ex. B, Sanofi_04878450 at 4; Ex. C, Sanofi_01268143 at 12, Ex. D, Palatinsky Dep. 444:14-445:9.
[2] Ex. E, Kessler Rep. at 20-21.
[3] Ex. F, Trial Tr. 432:4-433:2, Sept. 17, 2019; Ex. G. Kessler Dep. [Rough] 107:12-108:15, Nov. 26, 2019.
[4] Ex. H, Tosti Rep. at 12-17, Ex. I, Feigal Rep. at 55-60; Ex. J. Plunkett Rep. at 14-18; *see also* Ex. K, Madigan Rep. 20-26

these allegations, claiming that additional discovery would be necessary to address the prejudice posed by these new allegations. But these allegations are not new and have been a part of the "record" since December of 2018—a point which Defendants acknowledge. In addition, these allegations do not add a new claim or theory—rather, they further support Plaintiffs' Fraudulent Concealment claim as pled in Plaintiffs' Master Complaint.

Defendants' unfounded objections should be overruled.

Conclusion

Defendants seek to prevent Plaintiffs from (1) clarifying the definition of permanent hair loss that Defendants know is not based in fact and (2) adding detail to Plaintiffs' previously pled claim for fraudulent concealment. But Defendants suffer little, if at any, prejudice from Plaintiffs' proposed Third Amended Master Complaint. None of the allegations contained therein are "new" to Defendants and Defendants do not dispute the factual underpinnings. Defendants fail to offer a valid basis in which to deny Plaintiffs' proposed amendment under Rule 15A liberal standard for amending complaints.

Dated: December 3, 2019

Respectfully submitted,

/s/ Christopher L. Coffin
Christopher L. Coffin (#27902)
PENDLEY, BAUDIN & COFFIN, L.L.P.
1100 Poydras Street, Suite 2505
New Orleans, Louisiana 70163
Phone: (504) 355-0086
Fax: (504) 355-0089
ccoffin@pbclawfirm.com

Plaintiffs' Co-Lead Counsel

/s/ Karen B. Menzies
Karen Barth Menzies (CA Bar #180234)
Andre Mura (CA Bar # 298541)
GIBBS LAW GROUP LLP
6701 Center Drive West, Suite 1400
Los Angeles, California 90045
Telephone: 510-350-9700
Facsimile: 510-350-9701
kbm@classlawgroup.com

Plaintiffs' Co-Lead Counsel

/s/ M. Palmer Lambert
M. Palmer Lambert (#33228)
GAINSBURGH BENJAMIN DAVID
MEUNIER & WARSHAUER, LLC
2800 Energy Centre, 1100 Poydras Street
New Orleans, LA 70163-2800
Phone: 504-522-2304
Fax: 504-528-9973
plambert@gainsben.com

Plaintiffs' Co-Liaison Counsel

/s/ Dawn M. Barrios
Dawn M. Barrios (#2821)
BARRIOS, KINGSDORF & CASTEIX, LLP
701 Poydras Street, Suite 3650
New Orleans, LA 70139
Phone: 504-524-3300
Fax: 504-524-3313
barrios@bkc-law.com

Plaintiffs' Co-Liaison Counsel

PLAINTIFFS' STEERING COMMITTEE

Anne Andrews
Andrews Thornton Higgins Razmara, LLP
2 Corporate Park, Suite 110
Irvine, CA 92606
Phone: (800) 664-1734
aa@andrewsthornton.com

Daniel P. Markoff
Atkins & Markoff Law Firm
9211 Lake Hefner Parkway, Suite 104
Oklahoma City, OK 73120
Phone: (405) 607-8757
Fax: (405) 607-8749
dmarkoff@atkinsandmarkoff.com

J. Kyle Bachus
Bachus & Schanker, LLC
1899 Wynkoop Street, Suite 700
Denver, CO 80202
Phone: (303) 893-9800
Fax: (303) 893-9900
kyle.bachus@coloradolaw.net

Abby E. McClellan
Stueve Siegel Hanson LLP
460 Nichols Road, Suite 200
Kansas City, MO 64112
Phone: (816) 714-7100
Fax: (816) 714-7101
mcclellan@stuevesiegel.com

Lawrence J. Centola, III
Martzell, Bickford & Centola
338 Lafayette Street
New Orleans, LA 70130
Phone: (504) 581-9065
Fax: (504) 581-7635
lcentola@mbfirm.com

Karen Barth Menzies
Gibbs Law Group LLP
6701 Center Drive West, Suite 1400
Los Angeles, California 90045
Phone: 510-350-9700
Fax: 510-350-9701
kbm@classlawgroup.com

Christopher L. Coffin
Pendley, Baudin & Coffin, L.L.P.
1100 Poydras Street, Suite 2505
New Orleans, Louisiana 70163
Phone: (504) 355-0086
Fax: (504) 355-0089
ccoffin@pbclawfirm.com

David F. Miceli
David F. Miceli, LLC
P.O. Box 2519
Carrollton, GA 30112
Phone: (404) 915-8886
dmiceli@miceli-law.com

Alexander G. Dwyer
Kirkendall Dwyer LLP
440 Louisiana, Suite 1901
Houston, TX 77002
Phone: (713) 522-3529
Fax: (713) 495-2331
adwyer@kirkendalldwyer.com

Rand P. Nolen
Fleming, Nolen & Jez, L.L.P.
2800 Post Oak Blvd., Suite 4000
Houston, TX 77056
Phone: (713) 621-7944
Fax: (713) 621-9638
rand_nolen@fleming-law.com

Emily C. Jeffcott
Morgan & Morgan
700 S. Palafox Street, Suite 95
Pensacola, Florida 32505
Phone: (850) 316-9074
Fax: (850) 316-9079
ejeffcott@forthepeople.com

Hunter J. Shkolnik
Napoli Shkolnik PLLC
360 Lexington Avenue, 11th Floor
New York, NY 10017
Phone: (212) 397-1000
hunter@napolilaw.com

Andrew Lemmon
Lemmon Law Firm, LLC
P.O. Box 904
15058 River Road
Hahnville, LA 70057
Phone: (985) 783-6789
Fax: (985) 783-1333
andrew@lemmonlawfirm.com

Genevieve Zimmerman
Meshbesher & Spence Ltd.
1616 Park Avenue South
Minneapolis, MN 55404
Phone: (612) 339-9121
Fax: (612) 339-9188
gzimmerman@meshbesher.com

CERTIFICATE OF SERVICE

I hereby certify that on December 3, 2019, I electronically filed the foregoing with the Clerk of Court by using the CM/ECF system which will send a notice of electronic filing to all counsel of record who are CM/ECF participants.

/s/ M. Palmer Lambert
M. PALMER LAMBERT

EXHIBITS A – K
(UNDER SEAL)

Exhibit A

sanofi aventis

CLINICAL OVERVIEW DOCETAXEL - PERSISTENT ALOPECIA

Date: 18-Jan-2011 Total No. of pages: 45 Author: Emanuel Palatinsky, MD

Property of the sanofi-aventis group - strictly confidential
According to template: QSD-002592 VERSION N°1.0 (20-OCT-2009)

Outcome	Solicited Cases	Unsolicited Cases	ALL CASES
Recovered/Recovering/Recovered w/sequelae	122	226	348
Not recovered	102	110[a]	212
Total	**1,024**	**596**	**1,620**

[a]Case 2010SA051472 was erroneously captured with outcome unknown in PV database, but appears correctly in table above.

The 1,060 cases reporting an unknown outcome of the alopecia include 3 reports (1 solicited, and 2 unsolicited) where a "fatal" outcome of alopecia was entered in the database. All these 3 cases (JP01-00292, EG01-00001, and JP01-02889), however, reported a fatal outcome due to the underlying cancer. In any event, the cases where the outcome of alopecia was unknown will not be discussed further.

The remaining 560 (224 solicited, and 336 unsolicited) cases with a reported outcome were further reviewed to determine if, based on the available information and a sufficiently long outcome, the report met (or nearly met[1]) the definition of persistent alopecia: not recovered ≥12 months following the last dose of chemotherapy.

In 418 cases, the latest outcome was reported less than 12 months following the last dose of chemotherapy.

The remaining 142 cases (23 solicited and 119 unsolicited) were identified as cases reporting an outcome of alopecia at least 12 months following the last dose of chemotherapy (*i.e.*, they all met or nearly met the definition of persistent alopecia). Of these 142 cases, 24 reports of persistent alopecia did not have sufficient information (*e.g.*, prior of concurrent anti-cancer treatments) for a medical assessment and are summarized separately in table 2. The CIOMS files for these 142 cases are provided in Appendix 1, *pg. 047* .

[1] A report "nearly" met the definition of persistent alopecia if the alopecia was reported as not recovered without a specified duration of time (no calendar date), but with sufficient information in the case narrative to evince that it had not recovered for "*11 months*", or "*about 1 year*", "*almost 1 year*", etc. (considered sufficiently close to the 12 months needed for the definition of persistent alopecia) following the last dose of chemotherapy.

Property of the sanofi-aventis group - strictly confidential

Confidential Sanofi_04353215

Exhibit B

From: Hangai, Nanae R&D/US
Sent: Wednesday, April 08, 2015 5:52 PM
To: Atluri, Sarada R&D/US
Cc: Grenke, Rebecca R&D/US; Jen, Shang R&D/US; Urbancik, Gregory PH/US
Subject: RE: FDA Information Request: NDA 020449, TAXOTERE® (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL

Dear Sarada,

Thank you.
Please use the one I attached.
I corrected some spacing and typo.

What should I do the date and title??

Nana

From: Atluri, Sarada R&D/US
Sent: Wednesday, April 08, 2015 1:38 PM
To: Hangai, Nanae R&D/US
Cc: Grenke, Rebecca R&D/US; Jen, Shang R&D/US
Subject: RE: FDA Information Request: NDA 020449, TAXOTERE® (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL

It would help If I included it. Sorry!!

From: Hangai, Nanae R&D/US
Sent: Wednesday, April 08, 2015 1:37 PM
To: Atluri, Sarada R&D/US
Cc: Grenke, Rebecca R&D/US; Jen, Shang R&D/US
Subject: RE: FDA Information Request: NDA 020449, TAXOTERE® (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL

Dear Sarada,

Thank you, but where is the attachment??

N

From: Atluri, Sarada R&D/US
Sent: Wednesday, April 08, 2015 1:34 PM
To: Hangai, Nanae R&D/US
Cc: Grenke, Rebecca R&D/US; Jen, Shang R&D/US
Subject: RE: FDA Information Request: NDA 020449, TAXOTERE® (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL

Hi Nanae,

Confidential Sanofi_04878450

I transferred all the info into a template. Please review the attached document and let me know if its ok and ready to be uploaded into DOMASYS. Please send any corresponding dcuments that are needed for this submission.

Best regards,
Sarada

From: Hangai, Nanae R&D/US
Sent: Wednesday, April 08, 2015 11:31 AM
To: Atluri, Sarada R&D/US
Cc: Grenke, Rebecca R&D/US
Subject: FW: FDA Information Request: NDA 020449, TAXOTERE® (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL
Importance: High

Dear Sarada,

Please use this one.

I found MedDRA version should be 17.1, not 18.0
I corrected.
Nana

From: Hangai, Nanae R&D/US
Sent: Wednesday, April 08, 2015 10:51 AM
To: Atluri, Sarada R&D/US; Grenke, Rebecca R&D/US
Cc: Urbancik, Gregory PH/US; Polizzano, Frances R&D/US; Jen, Shang R&D/US
Subject: FW: FDA Information Request: NDA 020449, TAXOTERE® (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL

Dear Sarada and Rebecca,

Please find final clean version of document for FDA.

Warm regards,
Nana

From: Gupta, Sunil R&D/US
Sent: Wednesday, April 08, 2015 10:34 AM
To: Hangai, Nanae R&D/US
Subject: RE: FDA Information Request: NDA 020449, TAXOTERE® (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL

I will look through it within the next hour

Sunil Gupta, MD
Associate Vice-President,
Global Regulatory Affairs
Sanofi Oncology
Off: +1(617) 768-6613; Cell: (484) 557-8362
email: sunil.gupta@sanofi.com
500 Kendall Street, Cambridge, Massachusetts 02142. USA

Confidential

From: Hangai, Nanae R&D/US
Sent: Wednesday, April 08, 2015 10:32 AM
To: Gupta, Sunil R&D/US
Cc: Urbancik, Gregory PH/US; Ray, Pranav PH/US; Jen, Shang R&D/US; Grenke, Rebecca R&D/US; Atluri, Sarada R&D/US; Polizzano, Frances R&D/US
Subject: FW: FDA Information Request: NDA 020449, TAXOTERE® (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL

Dear Sunil

Did you have a chance to look at updated version?
Gregory found one missing character as below, I corrected.
If you do agree the updated version, we will process the document to meet the timeline.
Please let us know.

Warm regards,
Nana

Nanae Hangai, MD PhD
Global Safety Officer
SSRM Oncology Group
Global Pharmacovigilance and Epidemiology
Sanofi

617-768-6084
nanae.hangai@sanofi.com

From: Urbancik, Gregory PH/US
Sent: Wednesday, April 08, 2015 10:25 AM
To: Hangai, Nanae R&D/US
Subject: RE: FDA Information Request: NDA 020449, TAXOTERE® (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL

Nana,

I noticed in the last paragraph, trial was spelled incorrectly and the phase was left out.

GEICAM 9806 study was a randomized phase III trial comparing docetaxel in combination with

Gregory T. Urbancik
Global Regulatory Affairs, Oncology
sanofi-aventis U.S. LLC, A SANOFI COMPANY

From: Hangai, Nanae R&D/US
Sent: Tuesday, April 07, 2015 9:05 PM
To: Gupta, Sunil R&D/US; Polizzano, Frances R&D/US; Urbancik, Gregory PH/US
Cc: Ray, Pranav PH/US; Jen, Shang R&D/US; Grenke, Rebecca R&D/US
Subject: RE: FDA Information Request: NDA 020449, TAXOTERE® (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL

Dear All,

Please find enclosed revised version upon Sunil's comments.

After detail review of long standing alopecia cases again, I consider alopecia lasting more than 2 years with not recovered outcome as "permanent" alopecia.
Now total 89 cases are considered as "Permanent" alopecia.

Nana

Nanae Hangai, MD PhD
Global Safety Officer
SSRM Oncology Group
Global Pharmacovigilance and Epidemiology
Sanofi

617-768-6084
nanae.hangai@sanofi.com

From: Gupta, Sunil R&D/US
Sent: Tuesday, April 07, 2015 10:55 AM
To: Hangai, Nanae R&D/US; Polizzano, Frances R&D/US; Urbancik, Gregory PH/US
Cc: Ray, Pranav PH/US; Jen, Shang R&D/US; Grenke, Rebecca R&D/US
Subject: RE: FDA Information Request: NDA 020449, TAXOTERE® (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL

My comments on this document

Sunil Gupta, MD
Associate Vice-President,
Global Regulatory Affairs
Sanofi Oncology
Off: +1(617) 768-6613; Cell: (484) 557-8362
email: sunil.gupta@sanofi.com
500 Kendall Street, Cambridge, Massachusetts 02142. USA

From: Hangai, Nanae R&D/US
Sent: Tuesday, April 07, 2015 9:40 AM
To: Polizzano, Frances R&D/US; Urbancik, Gregory PH/US
Cc: Ray, Pranav PH/US; Jen, Shang R&D/US; Grenke, Rebecca R&D/US; Gupta, Sunil R&D/US
Subject: RE: FDA Information Request: NDA 020449, TAXOTERE® (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL

Dear Greg and Fran

Please find enclosed document regarding FDA request for permanent alopecia associated with docetaxel.

Warm regards,
Nana

Confidential

From: Polizzano, Frances R&D/US
Sent: Thursday, April 02, 2015 2:00 PM
To: Hangai, Nanae R&D/US
Cc: Gupta, Sunil R&D/US; Ray, Pranav PH/US; Urbancik, Gregory PH/US; Jen, Shang R&D/US; Grenke, Rebecca R&D/US
Subject: RE: FDA Information Request: NDA 020449, TAXOTERE® (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL

Hi Nana,

As I will be out of the office from April 3rd through April 12th, could you please send GPE's summary of permanent partial or total alopecia associated with docetaxel use to everyone on this email when the document is finalized. In my absence, Greg Urbancik will send the summary document to the FDA via email and official submission next Friday (April 10th). Becky Grenke will be the publisher in Regulatory Operations for this submission. Please provide the finalized summary document to Becky by next Wednesday (April 8th).

If you have any questions, please let Greg know.

Thanks,
Fran

From: Hangai, Nanae R&D/US
Sent: Wednesday, April 01, 2015 9:28 AM
To: Polizzano, Frances R&D/US
Cc: Gupta, Sunil R&D/US; Ray, Pranav PH/US; Urbancik, Gregory PH/US; Jen, Shang R&D/US
Subject: RE: FDA Information Request: NDA 020449, TAXOTERE® (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL

I am working on it.
I'm writing right now.

Nana

From: Polizzano, Frances R&D/US
Sent: Wednesday, April 01, 2015 9:22 AM
To: Hangai, Nanae R&D/US
Cc: Gupta, Sunil R&D/US; Ray, Pranav PH/US; Urbancik, Gregory PH/US; Jen, Shang R&D/US
Subject: RE: FDA Information Request: NDA 020449, TAXOTERE® (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL

Hi Nana,

Can you please provide a status update on the summary of cases of permanent partial or total alopecia associated with docetaxel use requested by the FDA?

Thanks,
Fran

From: Hangai, Nanae R&D/US
Sent: Monday, March 23, 2015 10:45 AM
To: Polizzano, Frances R&D/US
Cc: Gupta, Sunil R&D/US; Ray, Pranav PH/US; Urbancik, Gregory PH/US; Jen, Shang R&D/US
Subject: RE: FDA Information Request: NDA 020449, TAXOTERE® (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL

Dear Fran,

I got it, I and shang will work on this issue and provide the output ASAP,

Nana

From: Polizzano, Frances R&D/US
Sent: Monday, March 23, 2015 10:33 AM
To: Hangai, Nanae R&D/US
Cc: Gupta, Sunil R&D/US; Ray, Pranav PH/US; Urbancik, Gregory PH/US
Subject: FW: FDA Information Request: NDA 020449, TAXOTERE® (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL
Importance: High

Hi Nanae,

As discussed, the FDA is requesting a summary of cases of permanent partial or total alopecia associated with docetaxel use. The deadline for Sanofi's response is Friday, April 10th by close of business. In order to meet this timeline for the official submission, Regulatory Operations will need to receive GPE's summary of these cases by Wednesday, April 8th.

Please let me know if you have any questions.

Thanks,
Fran

From: Cross Jr, Frank H [mailto:Frank.CrossJr@fda.hhs.gov]
Sent: Monday, March 23, 2015 8:59 AM
To: Polizzano, Frances R&D/US
Subject: FDA Information Request: NDA 020449, TAXOTERE® (docetaxel) Injection Concentrate, 20 mg/mL and 80 mg/4 mL
Importance: High

Dear Dr. Polizzano,

By return e-mail and official submission, please provide your response by COB, EDT, April 10, 2015, to the following:

Please provide a summary of cases of permanent partial or total alopecia associated with docetaxel use.

Sincerely,

Frank Cross, Jr.

Frank Cross, Jr., MA, MT (ASCP)
Senior Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
White Oak Bldg 22, 2nd floor, Room 2110
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0876 (office)

(301) 796-9845 (fax)
(301) 796-2330 (Division Main #)
frank.crossjr@fda.hhs.gov

This e-mail and any accompanying attachments may be privileged, confidential, contain protected health information about an identified patient or be otherwise protected from disclosure. State and federal law protect the confidentiality of this information. If the reader of this message is not the intended recipient; you are prohibited from using, disclosing, reproducing or distributing this information; you should immediately notify the sender by telephone or e-mail and delete this e-mail.

Exhibit C

SANOFI

2.5 CLINICAL OVERVIEW: DOCETAXEL AND PERMANENT ALOPECIA

Author(s): Nanae Hangai, MD, PhD

Date: 11-Nov-2015 Total number of pages: 37

Confidential Sanofi_01268143

Preferred Term	Cases

There were 1 194 solicited cases and 978 unsolicited cases. For the unsolicited cases, 711 were reported from health care professionals (HCP) and 267 were from consumers. One thousand six-hundred eighty-two (1 682) cases reported female patients, 345 cases reported male patients, and 140 cases reported either unknown gender or were blank.

Docetaxel indication was reported in 2 022 cases. The most reported indication, when specific primary site was noted, was "breast cancer" including any kinds (n=1,358 (62.5%)) followed by any "lung cancer" excluding small cell lung cancer (n=278 (12.7%)), any "prostate cancer" (n=77 (3.5%)), any "gastric cancer" (n=52 (2.3%)), any "ovarian cancer" (n=41 (1.8%)), any "head and neck cancer" (n=26 (1.1%)), and any "oesophageal cancer" (n=26 (1.1%)).

The case outcomes for alopecia are shown in Table 3. The majority (60.7%) of cases reported unknown outcome.

Table 3 - Case outcomes

Outcome	Solicited	Unsolicited	All
Unknown*	900	420	1 320
Not recovered	136	254	390
Recovering	95	184	279
Recovered	55	81	136
Recovered w/ sequelae	6	36	42
Fatal**	1	3	4
Stabilized	1	0	1
Total	**1194**	**978**	**2172**

*includes blank

**Fatal outcome reported to other ADRs, cause of death was reported other medical condition.

5.3.2.1 Permanent alopecia

One hundred and seventeen (117) cases (5.3%) reported a verbatim event that included either "permanent" or "irreversible", or alopecia that lasted more than 2 years with an outcome of not recovered/recovering/unknown. Ninety six (96) cases were unsolicited reports; 73 from HCPs (including 10 literature cases) and 23 from consumers. One hundred and six (106) cases reported female patients and 11 cases did not specify the gender. Ninety-nine (99) cases (84.6%) reported any type of breast cancer as the indication for docetaxel, 1 case reported ovarian cancer, and remaining cases did not specify. The majority of cases received combination chemotherapy regimens (n=82 (70.0%)). The commonly used regimens were FEC-T (5-fluorouracil, epirubicin, cyclophosphamide followed by docetaxel) (n=46 (39.3%)), AC-T (doxorubicin, cyclophosphamide followed by docetaxel) (n=9 (7.6%)), EC-T (epirubicin, cyclophosphamide followed by docetaxel) (n=5 (4.2%)), TCH (docetaxel, carboplatin, trastuzumab) (n=5 (4.2%)), and TAC (docetaxel, doxorubicin, cyclophosphamide) (n=4 (3.4%)). Some of patients who

Exhibit D

UNITED STATES DISTRICT COURT

EASTERN DISTRICT OF LOUISIANA

****

IN RE: TAXOTERE (DOCETAXEL) MDL NO. 2740

PRODUCTS LIABILITY LITIGATION SECTION H

THIS DOCUMENT RELATES TO: JUDGE MILAZZO

ALL CASES MAG. JUDGE NORTH

****

VIDEOTAPED DEPOSITION OF:

EMANUEL PALATINSKY, M.D.

ROPES & GRAY LLP

Prudential Tower

800 Boylston Street

Boston, Massachusetts

August 10, 2018 8:38 a.m.

Darlene M. Coppola

Registered Merit Reporter

Certified Realtime Reporter

A. No, I cannot recall the details.

Q. Do you recall a story that was published in a newspaper covering some women who were complaining about having not been warned of but yet having ended up with alopecia of a permanent nature?

MR. RATLIFF: Object to form.

A. I recall some details about a story, but I don't remember the content of the story.

And it's normal that -- in response to your previous question, it's normal that the company wants to respond to this type of news.

BY MR. BACHUS:

Q. All right. In your -- in your e-mail, you make the statement in the second sentence that, "Even if we make the reasonable assumption that persistent alopecia after more than four years is consistent with permanent alopecia."

Do you see that?

A. Yes, I can see what I wrote.

Q. You agree with that, that it's reasonable to assume that alopecia that persists for more than four years is consistent with a definition of permanent

alopecia?

A. It was an assumption. It was a reasonable assumption.

Q. And I'm asking you, during your time as global safety officer you agreed with that?

A. I agreed --

Q. You wrote it?

A. -- that it was a reasonable assumption.

Q. All right. You go on to say, "I cannot estimate the general incidents rate of permanent alopecia when docetaxel is administered in combination with other chemotherapy agents based on the basis of only two studies."

Do you see that?

A. Yes, I can see what I wrote.

Q. And then you say, "I cannot say more than 'persistent alopecia' was reported in 3 to 6 percent of patients in two studies where adjuvant docetaxel was administered in combination with doxorubicin and cyclophosphamide for breast cancer."

That's what you said, right?

A. I wrote that.

Exhibit E

EXPERT REPORT

DAVID A. KESSLER, M.D.

information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of the actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study."[76]

78. If a drug manufacturer states on the label that a drug has risks that are similar to other drugs in its class, but in fact there are scientific data that indicate that the drug has increased risk compared to other drugs in the class, that label would be false or misleading under the Food, Drug, and Cosmetic Act.

V. KEY DEFINITIONS

79. The National Cancer Institute at the National Institutes of Health defines alopecia as "[t]he lack of hair from areas of the body where hair is usually found. Alopecia can be a side effect of some cancer treatments."[77]

80. According to a Sanofi leaflet distributed to healthcare providers, alopecia "is another word for hair loss or thinning of the hair. It is a common, yet temporary, side effect of some cancer medicines. Alopecia can occur anywhere on the body and may happen after a few treatments."[78]

81. With respect to irreversible alopecia, the medical literature has generally defined this condition as the "complete loss of growth or partial regrowth at least 6 months after chemotherapy."[79]

---

[76] *Id.*

[77] National Cancer Institute Diction of Cancer Terms, *available at* https://www.cancer.gov/publications/dictionaries/cancer-terms/def/alopecia (last visited Sep. 21, 2016).

[78] (Sanofi_01038470 at 5).

[79] *See, e.g.*, Kim G, Kim S, Park H. et al. (2017). Chemotherapy-induced irreversible alopecia in early breast cancer patients. Breast Cancer Res Treat 163:527-533; Namini S. (2016). Systematic Review of the Risk of Permanent Alopecia with Docetaxel Treatment for Breast Cancer. J Clin Case Rep 6(8); Haider M, Hamadah I, Almutawa A.

82. Over the last decade, Sanofi has defined irreversible alopecia multiple ways.

83. In an email dated March 16, 2010 regarding the social media communication plan for Taxotere, Sanofi's Global Safety Officer, Dr. Emanuel Palatinksy, wrote it was reasonable to consider alopecia permanent if the alopecia lasted for more than four years following treatment with Taxotere.[80]

84. In Sanofi's Periodic Safety Update Report ("PSUR") dated January 18, 2011, Sanofi attached Appendix 13 titled "Clinical Overview Docetaxel – Persistent Alopecia," which defined "persistent alopecia" as "alopecia nor[sic] recovered after 12 months from the end of a chemotherapy regimen than included docetaxel."[81]

85. Sanofi subsequently changed its definition, stating that irreversible alopecia is "alopecia lasting more than 2 years"[82] in response to a March 23, 2015 request by FDA for a summary of irreversible alopecia cases associated with Taxotere use.[83]

VI. IRREVERSIBLE ALOPECIA MEETS FDA CRITERIA OF "SERIOUS" AND/OR "CLINICALY SIGNIFICANT"

86. As noted above, under FDA regulations, the Warnings and Precautions section of drug labels must include serious and/or clinically significant adverse events"[84]

(2013). Radiation- and Chemotherapy-Induced Permanent Alopecia: Case Series. J Cutaneous Med & Surgery 17(1):55-61; Kluger N, Jacot W, Frouin E. et al. (2012). Permanent scalp alopecia related to breast cancer chemotherapy by sequential fluorouracil/ epirubicin/ cyclophosphamide (FEC) and docetaxel: a prospective study of 20 patients. Annals of Oncology 23(11):2879-2884; Tallon B. Blanchard E. Goldberg L. (2010). Permanent chemotherapy-induced alopecia: Case report and review of the literature. J Am Acad Dermatol 63:333-6; *see also* Sanofi_01021777 at 1.

[80] (Sanofi_05252079 at 2); *see also* Emanuel Palatinksy, M.D. Dep. 443:15-445:09.

[81] (Sanofi_00197757 at 8); (Sanofi_01397018 at 2); (Sanofi_05059757 at 1); Emanuel Palatinksy, M.D. Dep. 291:16-294:09.

[82] (Sanofi_04878450 at 4; *see also* (Sanofi_01021777 at 1); (Sanofi_00800098 at 3); (Sanofi_02664951); (Sanofi_01268180 at 35).

[83] (Sanofi_04878450 at 7); (Sanofi_01268180 at 8).

[84] 21 C.F.R. § 201.57(c)(6).

Exhibit F

UNITED STATES DISTRICT COURT

EASTERN DISTRICT OF LOUISIANA

IN RE: TAXOTERE (DOCETAXEL) PRODUCTS LIABILITY LITIGATION * Docket No.: 16-MD-2740 * Section "H(5)" * New Orleans, Louisiana * September 17, 2019

Relates to: Barbara Earnest *Case No.: 16-CV-17144*

* * * * * * * * * * * * * * * * * * *

DAY 2 - AFTERNOON SESSION
TRANSCRIPT OF JURY TRIAL BEFORE
THE HONORABLE JANE T. MILAZZO
UNITED STATES DISTRICT JUDGE

APPEARANCES:

For the Plaintiffs: Barrios Kingsdorf & Casteix, LLP
BY: DAWN M. BARRIOS, ESQ.
701 Poydras Street
Suite 3650
New Orleans, Louisiana 70139

For the Plaintiffs: Gainsburgh Benjamin David Meunier & Warshauer, LLC
BY: M. PALMER LAMBERT, ESQ.
1100 Poydras Street
Suite 2800
New Orleans, Louisiana 70163

For the Plaintiffs: Pendley Baudin & Coffin, LLP
BY: CHRISTOPHER L. COFFIN, ESQ.
1100 Poydras Street
Suite 2505
New Orleans, Louisiana 70163

APPEARANCES:

For the Plaintiffs: Gibbs Law Group, LLP
BY: KAREN BARTH MENZIES, ESQ.
6701 Center Drive West
Suite 1400
Los Angeles, California 90045

For the Plaintiffs: Bachus & Schanker, LLC
BY: J. KYLE BACHUS, ESQ.
DARIN L. SCHANKER, ESQ.
1899 Wynkoop Street
Suite 700
Denver, Colorado 80202

For the Plaintiffs: Fleming Nolen & Jez, LLP
BY: RAND P. NOLEN, ESQ.
2800 Post Oak Boulevard
Suite 4000
Houston, Texas 77056

For the Plaintiffs: DAVID F. MICELI, LLC
BY: DAVID F. MICELI, ESQ.
Post Office Box 2519
Carrollton, Georgia 30112

For the Plaintiffs: Morgan & Morgan, P.A.
BY: EMILY C. JEFFCOTT, ESQ.
700 S. Palafox Street
Suite 95
Pensacola, Florida 32502

For the Sanofi Defendants: Irwin Fritchie Urquhart & Moore, LLC
BY: DOUGLAS J. MOORE, ESQ.
400 Poydras Street
Suite 2700
New Orleans, Louisiana 70130

APPEARANCES:

For the Sanofi Defendants: Shook Hardy & Bacon, LLP
BY: HARLEY V. RATLIFF, ESQ.
JON A. STRONGMAN, ESQ.
2555 Grand Boulevard
Kansas City, Missouri 64108

For the Sanofi Defendants: Shook Hardy & Bacon, LLP
BY: HILDY M. SASTRE, ESQ.
201 Biscayne Boulevard, Suite 3200
Miami, Florida 33131

Official Court Reporter: Jodi Simcox, RMR, FCRR
500 Poydras Street
Room HB-275
New Orleans, Louisiana 70130
(504) 589-7780

Proceedings recorded by mechanical stenography, transcript produced by computer.

I N D E X

Taxotere labeling. Okay?
A. Happy to talk about this case.
Q. And one of the distinctions that was going on earlier was you were talking about alopecia and whether or not that covered temporary and permanent.
Do you remember that?
A. I remember that very well, sir.
Q. Okay. And I think, in your report, you actually talked about the phrase "irreversible alopecia."
A. Several times, yes.
Q. Yeah. And you have a footnote that says these terms are kind of interchangeable, "irreversible," "permanent."
A. Yes. I think that's fair.
Q. Very good. And I want to make sure we're kind of talking on the same page here.
All right. So in your report, you actually offered up -- you have a section in your report called, I think, "Key Definitions."
A. I believe so.
Q. And in your --
A. Would you like me to look -- turn to it?
Q. You certainly may.
A. Tell me what page.
Q. Paragraph 81.
A. Thank you, sir. Very kind.

Q. Are you with me?
A. I am, sir. Thank you.
Q. All right. In your report, in paragraph 81, what you say is "With respect to irreversible alopecia, the medical literature has generally defined this condition as the complete loss of growth or partial regrowth at least six months after chemotherapy." Correct?
A. Correct. And then I go on.
MR. NOLEN: Your Honor, may we approach?
THE COURT: Yes.
(WHEREUPON, the following proceedings were held at the bench.)
MR. NOLEN: Your Honor, Mr. Strongman is asking the witness questions about what is in the witness's expert report, and the report is not admitted into evidence. It will never be admitted into evidence.
The only thing the jury hears is what the jury heard today in his direct testimony. If he has questions that he wants to ask to try to impeach Dr. Kessler's opinions about the opinions he offered in this courtroom today, I think that's appropriate.
I don't think -- they got to depose him after he rendered his opinions. I don't think going into an expert's underlying report and what he did not offer in this courtroom is appropriate.

MR. STRONGMAN: I don't see how me simply asking how he defined the condition that it is he's saying we should have put in our label and in his report is in any way improper.
MR. NOLEN: I simply don't know how far it's going to go.
THE COURT: Well, I will tell you this, and I think -- this is an expert --
MR. NOLEN: I agree.
THE COURT: -- and I give a lot of latitude in cross-examination of experts. I don't know where this is going.
I think if he begins -- I think he can certainly ask him a question of how do you define the condition on which he's rendering his opinions. I don't know if we need to reference the report. It could be that you could just easily ask him, "Tell me what you think permanent alopecia is."
MR. STRONGMAN: I can do that, and I guess if he disagrees with me, that was part of why I didn't start with the report, to make it easier.
THE COURT: Of course. Of course.
MR. STRONGMAN: Easy enough.
THE COURT: I think it's fair, and it's certainly an appropriate question.
(WHEREUPON, the following proceedings were held in open court.)

BY MR. STRONGMAN:
Q. Ready to proceed?
A. I am.
Q. Very good. So, Doctor, you can agree with me that your definition of "irreversible alopecia" is -- in the medical literature, it was generally defined as six months with complete loss of growth or partial regrowth; correct?
A. I said the medical literature has generally defined it, right, but do note some exceptions to that.
Q. Very good. So there are -- there are several other definitions in the literature as well; correct?
A. Fair. Certainly within Sanofi, et cetera. And different doctors, different publications have different definitions.
Q. And, for example, we've seen definitions that go out to 12 months or 24 months, things like that; correct?
A. Correct.
Q. Okay. But you would agree with me that, most of the time in the literature, it's six months. That's the most common?
A. I think that's a reasonable period of time. There's no -- there's no magic to these numbers.
Q. Okay. And what we saw also in the literature is -- I doubt you saw any definition for what you're calling irreversible alopecia as being less than six months?
A. I think that would be correct because, in general, you know, before 2000, it was always expected, you know, that hair

would grow back. But sometimes it would take three to six months for that to happen.

Q. Okay. And with that kind of framework, we've kind of got some working definition here. I want to talk a little bit about what is in the labeling. Okay?

A. Sure.

Q. Okay. And --

MR. STRONGMAN: May I approach, Your Honor?

THE COURT: Yes, you may.

THE WITNESS: Thank you, Counsel.

BY MR. STRONGMAN:

Q. Of course. Doctor, what I've handed you has been marked as Defendants' Exhibit 215.

And this is the 1996 approval letter from the FDA; correct?

A. Correct, signed by Dr. Temple.

MR. STRONGMAN: And Sanofi would move into evidence Defendants' Exhibit 215.

THE COURT: Any objection?

MR. NOLEN: No objection, Your Honor.

THE COURT: Let it be admitted.

BY MR. STRONGMAN:

Q. Okay. And, Doctor, with the approval letter that we've got here, Defendants' Exhibit 215, there's also the labeling attached; correct?

A. Correct.

Q. Okay. And as we know, earlier when you were testifying about time frames, I think you may have said something about 2009, maybe 2006, in terms of when a label should have been changed.

Do you remember that?

A. When there was evidence of a -- association or causal association, yes.

Q. But we can certainly agree that you're not offering any opinions that there was an inadequacy with regard to any kind of hair-loss warning in the 1996 label; correct?

A. That would be correct, yes.

MR. STRONGMAN: May I approach, Your Honor?

THE COURT: Sure.

BY MR. STRONGMAN:

Q. Doctor, I'm going to hand you what I've marked as Defense Exhibit 317. If you could take a look at that.

A. Yes.

Q. And this is the approval letter from the FDA for the 2004 Taxotere application; correct?

A. Correct.

Q. And included with the approval letter also is the labeling; is that correct?

A. Correct.

MR. STRONGMAN: Defendants would move into evidence

Defense Exhibit 317.

THE COURT: Any objection?

MR. NOLEN: No objection, Your Honor.

THE COURT: Let it be admitted.

BY MR. STRONGMAN:

Q. And, Doctor, we can also agree, based on what you said this morning, that you've not offered any opinions that the labeling for Taxotere, as it relates to hair loss, was inadequate in the 2004 labeling; correct?

A. That would be fair.

Q. And I asked you this already, but we can agree that the definition of "alopecia" -- you've been asked this -- it's hair loss; correct?

A. "Alopecia" means hair loss, correct.

Q. And we can agree that "alopecia" was always in the Taxotere label; correct?

A. "Alopecia" was in the Taxotere label.

Q. And if I take out Webster's dictionary and look up "alopecia," the definition will just be loss of hair; correct?

A. I'm sure that would be correct.

Q. And we talked about the American Cancer Society a little bit earlier.

Do you remember that?

A. Correct.

Q. And the American Cancer Society, we established, is a

reliable organization that puts out information into the public; correct?

A. Correct.

Q. And they put out information about how terms are defined; correct?

A. They put -- a lot of organizations may have glossaries or other things, yes.

MR. STRONGMAN: May I approach?

THE COURT: Yes, you may.

BY MR. STRONGMAN:

Q. Doctor, what I've handed you is entitled "The American Cancer Society Breast Cancer Dictionary."

Do you see that?

A. Thank you very much.

Q. Okay. It has a date of 2006 on it; correct?

A. I'll take you're representation. I'm sure it's here somewhere. I'm just not seeing it, but I'll take your representation.

MR. STRONGMAN: Permission to publish, Your Honor?

THE COURT: Is this in evidence?

MR. STRONGMAN: This is a learned treatise. It's a reliable publication by a reliable organization.

THE COURT: I think you're going to need to lay a foundation that's it's a learned treatise.

Exhibit G

VIDEO TECHNICIAN: At this time will the court reporter swear in the witness.

Whereupon,

DAVID A. KESSLER, M.D.,

being first duly sworn or affirmed to testify to the truth, the whole truth, and nothing but the truth, was examined and testified as follows:

EXAMINATION BY COUNSEL FOR SANOFI DEFENDANTS

BY MR. MCRAE:

Q. Good morning, doctor. Please state your full name and business address for the record?

A. 505 parnast avenue, San Francisco, California.

Q. My name is Chris and I represent Sanofi

Q. Okay. Now, in your original report, you defined irreversible alopecia as alopecia that has not resolved at least six months after chemotherapy treatment, right?

MS. JEFFCOTT: Object to form.

THE WITNESS: I think we can pull -- I think there's a footnote on that. I think that

I -- I mean, there are certain definitions, Sanofi has had... I acknowledged, if my memory serves me, about a year, two years. And I say when -- not otherwise,b we'd have to get the exact language.

If there's not the definition, you can assume it's six months.

But again, I think -- I do acknowledge there's multiple definitions.

BY MR. MCRAE:

Q. Sure. And I guess I was just asking, what's your definition? I understand there are multiple in the world. Dr. Kessler, what's yours?

A. Well, I think we should allow for purposes for trial for the clinical determination. Right? Six months, my experience the hair starts growing back six months after.

Q. Okay.

A. But I think the longer you give it, the more certainty there is.

Exhibit H

EXPERT REPORT OF

Antonella Tosti, M.D.

October 21, 2019

I am a Fredric Brandt Endowed Professor of Dermatology at the University of Miami. I have been involved in the diagnosis and treatment of hair disorders for more than 30 years and see hair patients on a daily basis in Miami and in Europe.

I was born and trained in Italy, and I was full Professor of Dermatology at the University of Bologna until 2010. I have been full Professor at University of Miami since then.

I am among the developers of a new non-invasive method for the diagnosis of hair and scalp disorders named dermoscopy or trichoscopy, and I published the first comprehensive paper on this topic in 2006.[1] I have published many peer reviewed articles on trichoscopy, including a recent article on trichoscopy of the black scalp[2] and the first book/atlas on hair and scalp dermoscopy with pathological correlations in 2007.[3] The book was translated in other languages and the 2nd edition of this book was published in 2015.[4] I have been invited to teach hair disorders and trichoscopy worldwide, and have trained hundreds of dermatologists to utilize this technique to properly examine their patients.[5]

I was president and founding member of the European Hair Research Society (1989) and am now president of the American Hair Research Society and president of the International Society of Trichoscopy. I am editor of 30 Textbooks, including 6 on diagnosis and treatment of Hair Disorders.

I am the author of more than 600 peer reviewed papers, with an h-index of 58 on Scopus.[6]

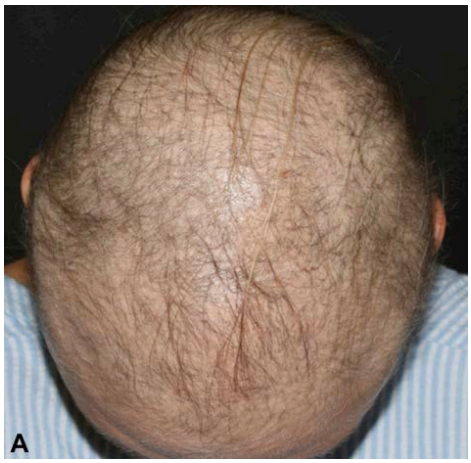
My Curriculum Vitae, fee schedule, and prior deposition testimony are attached as **Exhibits A**, **B**, and **C**, respectively.

---

[1] Elisabeth K. Ross, Colombina Vicenzi & Antonella Tosti, *Videodermoscopy in the Evaluation of Hair and Scalp Disorders*, 55(5) J. AM. ACAD. DERMATOL. 799 (2006).
[2] Jorge Ocampo-Garza & Antonella Tosti, *Trichoscopy of Dark Scalp*, 5(1) SKIN APPENDAGE DISORD. 1-8 (2019).
[3] Antonella Tosti, *Dermoscopy of Hair and Scalp Disorders: With Clinical and Pathological Correlations* (1st ed. 2007).
[4] Antonella Tosti (ed.), *Dermoscopy of the Hair and Nails* (2nd ed. 2015).
[5] *Antonella Tosti*, WIKIPEDIA, https://en.wikipedia.org/wiki/Antonella_Tosti (Nov. 5, 2018).
[6] In 2005, the h-index was proposed by Jorge Hirsch, PhD and published in the *Proceedings of the National Academy of Sciences of the United States of America*. Jorge E. Hirsch, *An Index to Quantify an Individual's Scientific Research Output*, 102(46) PROC. NATL. ACAD. SCI. U.S.A. 16569 (2005).
An h-index of 58 means that I have authored at least 58 publications that have each been cited at least 58 times. Professor Hirsch reckons that after 20 years of research, an h-index of 20 is good, 40 is outstanding, and 60 is truly exceptional. The advantage of the h-index is that it combines productivity (i.e., number of papers produced) and impact (number of citations) in a single number.

FPHL may be caused by hormonal therapies with androgenic effects. Hormone receptor positive breast cancer has estrogen and/or progesterone receptors. These cancers are commonly treated with endocrine therapy to lower estrogen levels, such as aromatase inhibitors, or to block estrogen's effects, such as Tamoxifen. Endocrine therapy can cause alopecia with a pattern similar to FPHL due to the miniaturization of the hair follicle.[17] Endocrine therapy is not associated with follicular loss. According to a recent study, alopecia from endocrine therapy develops several months after therapy initiation (mean 16.8 months) and is moderate (grade 1) in 92% of patients.[18]

Permanent Alopecia After Chemotherapy (Permanent Chemotherapy-Induced Alopecia – PCIA)



19

Permanent Alopecia After Chemotherapy (also known as Persistent Alopecia After Chemotherapy, Irreversible Alopecia after Chemotherapy, Permanent Chemotherapy-Induced Alopecia or PCIA) is defined as incomplete hair regrowth after chemotherapy.[20] The precise pathogenetic process is not known; however, it is likely due to the destruction or damage of the hair follicle or dermal papilla stem cells. This is a severe long-term side effect of chemotherapy that has been associated with high doses of chemotherapy in the context of bone marrow transplantation[21] and, in more recent years, has been consistently identified in the context of adjuvant chemotherapy regimens containing Taxotere/docetaxel for breast cancer.[22] PCIA was first reported in this context in 2001: a clinical trial investigated the efficacy and toxicity of Taxotere/docetaxel with doxorubicin and cyclophosphamide (TAC) as first-line chemotherapy

[17] *See* Azael Freites-Martinez, MD et al., *Endocrine Therapy-Induced Alopecia in Patients with Breast Cancer*, 154(6) JAMA DERMATOL. 670 (2018).
[18] *Id.*
[19] Azael Freites-Martinez, MD et al., *Hair Disorders in Cancer Survivors*, 80(5) J. AM. ACAD. DERMATOL. 1199-1213 (2019).
[20] Miguel Martín et al., *Persistent Major Alopecia Following Adjuvant Docetaxel for Breast Cancer: Incidence, Characteristics, and Prevention with Scalp Cooling*, 171(3) BREAST CANCER RES. TREAT. 627-34 (2018);
[21] *See, e.g.*, Antonella Tosti, MD et al., *Permanent Alopecia After Busulfan Chemotherapy*, 152 BRIT. J. DERMATOL. 1056 (2005).
[22] *See, e.g.*, Ben Tallon, MBChC et al., *Permanent Chemotherapy-Induced Alopecia: Case Report and Review of the Literature*, 63(2) J. AM. ACAD. DERMATOL. 333 (2010). For the complete list of articles and abstracts I reviewed and analyzed regarding permanent chemotherapy-induced alopecia in the context of adjuvant breast cancer chemotherapy, see **Exhibit E** – Articles on Permanent Alopecia Following Breast Cancer Chemotherapy.

for patients with metastatic breast cancer.[23] Of the 54 patients treated, long-lasting (longer than 2 years) alopecia occurred in 4 patients (7.4%).[24] Since then hundreds of cases have been described in the literature, and the clinical features and course of PCIA have been characterized by several retrospective and a few prospective studies.[25]

Patients with PCIA develop Anagen Effluvium from chemotherapy and have incomplete hair regrowth 6 to 8 months after the end of chemotherapy. Patients have moderate to very severe hair thinning, with short miniaturized hairs. Hair thinning is diffuse but can be more prominent on androgen-dependent scalp regions, and the condition can be misdiagnosed as Androgenetic Alopecia at clinical examination and at pathology, even though in PCIA there is often a reduction in the follicle number in addition to miniaturization. With PCIA, thinning of eyelashes and eyebrows and other body hairs is also typical.[26] PCIA is graded as 1 or 2 depending on severity (necessity to wear a wig = grade 2) and psychological impact according to the Common Terminology Criteria for AEs (CTCAE) Version 4.0.[27]

PCIA in patients receiving chemotherapy for breast cancer, outside the context of bone marrow transplantation, is a relatively new described disease: the first cases were described in 2001,[28] when Taxotere was introduced in the chemotherapy regimens. The other two chemotherapy agents that are commonly in Taxotere/docetaxel regimens—Adriamycin/doxorubicin (an anthracycline) and cyclophosphamide—have been on the market since 1974[29] and 1959.[30]

In the treatment of breast cancer, Taxotere/docetaxel are the only chemotherapy regimens that have been consistently shown to cause Permanent Chemotherapy-Induced Alopecia.[31] I have

---

[23] J.M. Nabholtz et al., *Phase II Study of Docetaxel, Doxorubicin, and Cyclophosphamide as First-Line Chemotherapy for Metastatic Breast Cancer*, 19(2) J. CLIN. ONCOL. 314-21 (2001).
[24] *Id.* at 318.
[25] *See, e.g.*, S.M. Sedlacek, *Persistent Significant Alopecia (PSA) from Adjuvant Docetaxel After Doxorubicin/Cyclophosphamide (AC) Chemotherapy in Women with Breast Cancer*, 100 BREAST CANCER RES. TREAT. s116 (2006); Ben Tallon, MBChC et al., *Permanent Chemotherapy-Induced Alopecia: Case Report and Review of the Literature*, 63(2) J. AM. ACAD. DERMATOL. 333 (2010); Antonella Tosti, MD et al., *Docetaxel and Permanent Alopecia*, 68(5) J. AM. ACAD. DERMATOL. e151 (2013); Miguel Martín et al., *Persistent Major Alopecia Following Adjuvant Docetaxel for Breast Cancer: Incidence, Characteristics, and Prevention with Scalp Cooling*, 171(3) BREAST CANCER RES. TREAT. 627-34 (2018); Danbee Kang et al., *Permanent Chemotherapy-Induced Alopecia in Patients with Breast Cancer: A 3-Year Prospective Cohort Study*, 23 THE ONCOLOGIST 1 (2018). For the complete list of articles and abstracts I reviewed and analyzed regarding permanent chemotherapy-induced alopecia in the context of adjuvant breast cancer chemotherapy, see **Exhibit E** – Articles on Permanent Alopecia Following Breast Cancer Chemotherapy.
[26] Nicolas Kluger et al., *Permanent Scalp Alopecia Related to Breast Cancer Chemotherapy by Sequential Fluorouracil/Epirubicin/Cyclophosphamide (FEC) and Docetaxel: A Prospective Study of 20 Patients*, 23 Annals of Oncology 2879 (2012).
[27] Azael Freites-Martinez, MD et al., *Assessment of Quality of Life and Treatment Outcomes of Patients with Persistent Postchemotherapy Alopecia*, JAMA DERMATOL. (published online March 6, 2019).
[28] J.M. Nabholtz et al., *Phase II Study of Docetaxel, Doxorubicin, and Cyclophosphamide as First-Line Chemotherapy for Metastatic Breast Cancer*, 19(2) J. CLIN. ONCOL. 314-21 (2001).
[29] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=050467.
[30] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=012141.
[31] J.M. Nabholtz et al., *Phase II Study of Docetaxel, Doxorubicin, and Cyclophosphamide as First-Line Chemotherapy for Metastatic Breast Cancer*, 19(2) J. CLIN. ONCOL. 314 (2001); Ben Tallon, MBChC et al., *Permanent Chemotherapy-Induced Alopecia: Case Report and Review of the Literature*, 63(2) J. AM. ACAD.

reviewed and analyzed 18 articles and abstracts regarding permanent chemotherapy-induced alopecia in the context of adjuvant breast cancer chemotherapy—17 of which report distinct cases of PCIA from Taxotere/docetaxel regimens, and 1 of which reports cases of PCIA from unidentified taxane (Taxotere or Taxol) regimens.[32] In the adjuvant treatment of breast cancer, there are only 39 cases of permanent alopecia reported with non-taxane regimens with anthracyclines and cyclophosphamide in comparison with 497 reported cases with taxane regimens—353 of which are Taxotere/docetaxel regimens.[33] Cases of alopecia lasting more than 6 months after the end of chemotherapy have been reported with the use of Taxotere in both combination and monotherapy.[34] There is consistent, sufficient, and reliable evidence that Taxotere/docetaxel, when used in regimens with anthracyclines and doxorubicin, is a substantially contributing factor to PCIA.[35]

I also co-authored an article published in 2019 in *JAMA Dermatology* that collected cases of PCIA from three cancer centers. These cases included patients who received chemotherapy for different types of cancer and not only breast cancer.[36] The aim of this study was evaluating the quality of life of patients with PCIA and not the frequency of PCIA from any of the regimens; therefore, this is not a prevalence study.[37] There were 80 cases of PCIA in regimens with Taxotere/docetaxel or Taxol/paclitaxel and 18 cases reported in regimens without Taxotere/docetaxel or Taxol/paclitaxel.[38] Taxotere/docetaxel and Taxol/paclitaxel are related drugs—referred to as taxanes. The study does not provide any information about the prevalence of PCIA from Taxotere/docetaxel versus Taxol/paclitaxel.

The studies I have analyzed in the aggregate demonstrate that Taxotere/docetaxel is far more commonly reported as being associated with PCIA than any other chemotherapy regimen.[39] I have also personally seen patients with PCIA from Taxotere/docetaxel regimens, but I have never seen patients with PCIA from Taxol/paclitaxel or other non-Taxotere regimens. I saw my first case of PCIA from Taxotere/docetaxel in 2006.

As a result of my analysis in the case, I learned that the randomized studies with Taxotere regimens for breast cancer—sponsored by the manufacturer, Sanofi, revealed that Taxotere

---

DERMATOL. 333 (2010); Antonella Tosti, MD et al., *Docetaxel and Permanent Alopecia*, 68(5) J. AM. ACAD. DERMATOL. e151 (2013). *See* **Exhibit E** – Articles on Permanent Alopecia Following Breast Cancer Chemotherapy.

[32] *See* **Exhibit E** – Articles on Permanent Alopecia Following Breast Cancer Chemotherapy.

[33] *See* **Exhibit E** – Articles on Permanent Alopecia Following Breast Cancer Chemotherapy. 349 cases were reported with Taxotere/docetaxel regimens, and 4 cases were reported with Taxotere/docetaxel and Taxol/paclitaxel regimens. 93 cases were reported with unidentified taxane regimens. Gun Min Kim et al., *Chemotherapy-Induced Irreversible Alopecia in Early Breast Cancer Patients*, 163 BREAST CANCER RES. TREAT. 527-33 (2017).

[34] H. Bourgeois, *Long Term Persistent Alopecia and Suboptimal Hair Regrowth After Adjuvant Chemotherapy for Breast Cancer*. 2009. *Long Term Persistent Alopecia and Suboptimal Hair Regrowth after Adjuvant Chemotherapy for Breast Cancer: Alert for Emerging Side Effect: French ALOPERS Observatory*, 21(8) ANNALS OF ONCOL. Viii83-84 (2010). 30(b)(6) Depositions of Michael Kopreski, MD, including all exhibits. Nanae Hangai, MD, PhD, Global Safety Officer, "Clinical Overview: Docetaxel and Permanent Alopecia" Sanofi_00829529-65.

[35] *See* **Exhibit E** – Articles on Permanent Alopecia Following Breast Cancer Chemotherapy.

[36] Azael Freites-Martinez, MD et al., *Assessment of Quality of Life and Treatment Outcomes of Patients with Persistent Postchemotherapy Alopecia*, JAMA DERMATOL. (published online March 6, 2019).

[37] *Id.*

[38] *Id.* at E3. Among the 80 cases, 47 were paclitaxel regimens, 31 were docetaxel regimens, and 2 were paclitaxel and docetaxel regimens.

[39] *See* **Exhibit E** – Articles on Permanent Alopecia Following Breast Cancer Chemotherapy.

regimens had a statistically increased rate of PCIA, when controlled for Adriamycin/doxorubicin and cyclophosphamide.[40]

I was able to review Sanofi's data analysis in 2015, which concluded that Taxotere/docetaxel chemotherapy regimens can cause permanent/irreversible alopecia:

> Upon review of safety database, 117 cases (5.3% of total cases of alopecia) were considered permanent alopecia (criteria: "permanent" or "irreversible" in verbatim event or longstanding (*more than 2 years*)) and have been reported in association with docetaxel treatment. . . .
>
> Based on review of the Sanofi global pharmacovigilance database, worldwide scientific literature, clinical studies, and biological plausibility, the *cumulative weighted evidence is sufficient to support a causal association between docetaxel and permanent/irreversible alopecia in the patients who received docetaxel*.[41]

There is consistent, sufficient, and reliable evidence that Taxotere/docetaxel, when used in in the same regimen as anthracyclines and doxorubicin, is a substantially contributing factor to PCIA.[42]

The three studies that compared AC regimens without Taxotere/docetaxel with regimens containing Taxotere/docetaxel showed a much greater frequency and severity of PCIA in the Taxotere/docetaxel regimens. These studies demonstrate that chemotherapy regimens that include Taxotere/docetaxel are the substantial contributing factor and that Taxotere/docetaxel is the causal variable for PCIA.

Sedlacek (2006)[43]

A retrospective prospective evaluation of consecutive treatment of 496 women with early-stage breast cancer was published in 2006. The patients were treated by Dr. Sedlacek from January 1994 through December of 2004. The chemotherapy regimens compared:

- Group A: 258 patients administered doxorubicin and cyclophosphamide regimens without taxanes (AC, FAC, A/CMF).

- Group B: 126 patients administered doxorubicin and cyclophosphamide plus paclitaxel/Taxol (AC/T, AT/T, AC/T dose dense, ATC, AC/Herceptin).

---

[40] TAX 316 Clinical Study Report (Jan. 21, 2004) at p. 5, Sanofi_02640584. TAX 316 Clinical Study Report (Sept. 9, 2010) at p. 37, Sanofi_02645236. GEICAM 9805 Clinical Study Report (Nov. 9, 2009) at 111, Sanofi_01061868.
[41] Nanae Hangai, MD, PhD, Global Safety Officer, "Clinical Overview: Docetaxel and Permanent Alopecia" Sanofi_00829563 (emphasis added).
[42] *See* **Exhibit E** – Articles on Permanent Alopecia Following Breast Cancer Chemotherapy.
[43] S.M. Sedlacek, *Persistent Significant Alopecia (PSA) from Adjuvant Docetaxel After Doxorubicin/Cyclophosphamide (AC) Chemotherapy in Women with Breast Cancer*, 100 BREAST CANCER RES. TREAT. s116 (2006).

- Group C: 112 patients administered doxorubicin and cyclophosphamide plus docetaxel/Taxotere (AC/Tax, ATax, ACTax, AC/TaxXeloda[44], AC/Tax Herceptin[45], ATax/FAC, FAC/Tax).

The average time from the last dose of chemotherapy was 48 months (range 19 to 85 months). Persistent significant alopecia, defined as <50% hair regrowth at least one year after chemotherapy, developed in 7/112 (6.3%) of women treated with a Taxotere/docetaxel/ doxorubicin/cyclophosphamide-containing regimen. All were reported to be wearing wigs. No persistent significant alopecia occurred in those treated with a Taxol/paclitaxel/doxorubicin/ cyclophosphamide-containing regimen, or in those treated with a doxorubicin/cyclophosphamide regimen without a taxane.

Kang et al. (2018)[46]

A prospective cohort study, from February 2012 to July 2013, was conducted of 61 consecutive patients with early stage breast cancer expected to receive adjuvant chemotherapy. The objective of the study was to estimate the long-term incidence of PCIA in patients whose hair volume and density were measured prior to chemotherapy and who were followed for three years after chemotherapy.

The patient groups received one of three regimens:

- AC (doxorubicin plus cyclophosphamide),
- FAC (fluorouracil plus cyclophosphamide and doxorubicin), or
- AC-T (Taxotere after AC).

Patients' hair was assessed prior to chemotherapy. Thereafter hair was assessed "on the first day of chemotherapy, after two cycles of chemotherapy, at 1, 3, and 6 months after completion of chemotherapy, and after 3 years after completion of chemotherapy."[47] At each visit, "hair density" and "shaft diameter" were "objectively quantified" using a dermatoscope.[48] The study defined PCIA as "absent or incomplete hair regrowth at ≥6 months after chemotherapy . . . if hair density or thickness was two standard deviations (SDs) or more below the baseline mean (before chemotherapy)."[49]

Additionally, the investigators ruled out a number of potential risk factors: "Patients with alopecia, atopic dermatitis, psoriasis, or infectious skin diseases, as well as patients who were taking steroids, antihistamines, antidepressants, or anticonvulsants were excluded from the study."[50]

---

[44] Xeloda (generic Capecitabine) is a chemotherapy drug that can cause temporary hair loss but has not been reported to cause permanent alopecia.
[45] Herceptin (generic Trastuzumab) is a targeted cancer drug that has not been reported to cause hair loss.
[46] Danbee Kang et al., *Permanent Chemotherapy-Induced Alopecia in Patients with Breast Cancer: A 3-Year Prospective Cohort Study*, 23 THE ONCOLOGIST 1 (2018).
[47] *Id* at 2.
[48] *Id.*
[49] *Id*.
[50] *Id.*

The study results demonstrated that Taxotere was strongly associated with PCIA: Patients with Taxotere-based treatment had "about eight times higher odds of PCIA 3 years after completion of chemotherapy (8.01; 95% CI, 1.20–53.26) adjusting for age, hair density, and thickness at diagnosis."[51] There were 23 cases of PCIA in the Taxotere group and only 3 with the cyclophosphamide and anthracycline groups.

Martín et al. (2018)[52]

492 breast cancer patients with adjuvant treatment for breast cancer were studied for the prevalence of PCIA in one institution in Spain between December 2005 and May 2006. Two other institutions in Spain joined the prevalence study later to confirm the prevalence of grade 2 permanent alopecia. Grade 2 permanent alopecia was defined as severe alopecia that requires a wig after at least 18 months from the end of chemotherapy. The median follow-up of patients after the end of chemotherapy was 43 months (range 18-60 months). Grade 2 PCIA only occurred in patients with Taxotere/docetaxel regimens.

The study also addressed the issue of whether regimens containing AC or EC cause permanent alopecia in the absence of Taxotere/docetaxel. In the 306 patients receiving other chemotherapy regimens (including AC/EC regimens alone or followed by Taxol/paclitaxel), there were no cases of grade 2 permanent alopecia. The study also looked at patients receiving endocrine therapy. There were no cases of permanent alopecia (even grade 1) in patients who received tamoxifen without chemotherapy. The incidence of Taxotere/docetaxel-induced grade 2 permanent alopecia was similar in patients with (22/221, 9.96%) and without endocrine therapy (14/137, 10.2%).

Diagnostic Ladder

I have attempted to review all of the medical records of the patient. The records reviewed are listed in **Exhibit D** — Materials Consulted.

On June 4, 2019, I was able to perform an in-person evaluation of Cynthia Thibodeaux, and the examination progress notes and photographs are attached as **Exhibit F**.

During my clinical examination of Ms. Thibodeaux, I took two scalp biopsies. Subsequently I received and considered the dermatopathology report of Curtis Thompson, MD, which is attached as **Exhibit G**.

1) History

Clinical history is very important for the correct assessment of hair disorders.

Cynthia Thibodeaux is a 73-year-old woman of African descent with a Caucasian grandfather who was diagnosed with early stage breast cancer in January 2008 at the age

[51] *Id.* at 3.
[52] Miguel Martín et al., *Persistent Major Alopecia Following Adjuvant Docetaxel for Breast Cancer: Incidence, Characteristics, and Prevention with Scalp Cooling*, 171(3) BREAST CANCER RES. TREAT. 627-34 (2018).

Exhibit I

Expert Report of Ellen G. Feigal, M.D.

MDL - 2740 Taxotere (Docetaxel) Products Liability Litigation

Eastern District of Louisiana United States District Court

D. Brief Narratives of Clinical Studies

Nabholtz (2001): A phase 2 single arm clinical trial investigated the efficacy and toxicity of Taxotere/docetaxel with doxorubicin and cyclophosphamide (TAC) as first-line chemotherapy for anthracycline-naïve patients with metastatic breast cancer. Of the 54 patients treated, the most common treatment-related chronic non-hematologic toxicity was alopecia, with long-lasting (longer than 2 years) partial alopecia occurring in 4 (7.4%) patients.

Bertrand (2013): A prospective clinical study of scalp cooling investigated 79 patients treated with fluorouracil, epirubicin, cyclophosphamide and docetaxel for early stage breast cancer between July 2005 and December 2007 were included in this study. All patients received scalp cooling during chemotherapy, and all patients underwent a clinical examination and photographs of the scalp 5 years after the end of chemotherapy. 26 patients (32.9%) had permanent alopecia, which was severe in 3 patients, moderate in 2 patients, and minimal in 21 patients.

Kang (2018): A prospective cohort study, from February 2012 to July 2013 was conducted at the Samsung Medical Center in Seoul, Korea, of 61 consecutive patients with early stage breast cancer expected to receive adjuvant chemotherapy at the outpatient breast cancer clinic. The objective of the study was to estimate the long-term incidence of permanent chemotherapy-induced alopecia (PCIA) in a cohort of patients with breast cancer whose hair volume and density were measured prior to chemotherapy and who were followed for 3 years after chemotherapy.

The patients received one of the following regimens: 1) doxorubicin and cyclophosphamide (AC); 2) fluorouracil plus cyclophosphamide and doxorubicin (FAC), or 3) doxorubicin and/or cyclophosphamide plus Taxotere/docetaxel). There were 32 patients who received a Taxotere-based regimen, and 29 who received an AC or FAC regimen.

Patients were assessed prior to chemotherapy on the first day of chemotherapy, after 2 cycles of chemotherapy, at 1, 3, and 6 months after completion of chemotherapy and at 3 years after completion of chemotherapy. At each visit, hair density and hair shaft diameter were objectively quantified by a phototrichogram using a Folliscope.[103] The study defined PCIA as

---

[103] Danbee Kang et al., *Permanent Chemotherapy-Induced Alopecia in Patients with Breast Cancer: A 3-Year Prospective Cohort Study*, 23 THE ONCOLOGIST 1-7, 2 (2018).

absent or incomplete hair regrowth at ≥6 months after chemotherapy. Incomplete hair regrowth was defined as hair density or thickness was two standard deviations (SDs) or more below the baseline mean (before chemotherapy).[104]

To isolate the impact of chemotherapy on PCIA, the study excluded patients at baseline who had alopecia, atopic dermatitis, psoriasis, or infectious skin diseases, as well as patients who were taking steroids, antihistamines, antidepressants, or anticonvulsants.[105]

The study results demonstrated that patients receiving Taxotere-based treatment had about eight times higher odds of PCIA 3 years after completion of chemotherapy (OR 8.01; 95% CI, 1.20–53.26, $p < .05$) adjusting for age, hair density, and thickness at diagnosis.[106] There were 23 cases of PCIA in the Taxotere/docetaxel group and only 3 with the AC regimens.

Martín (2018): 492 breast cancer patients with adjuvant treatment for breast cancer were studied for the prevalence of permanent chemotherapy-induced alopecia (PCIA) in 1 institution in Spain between December 2005 and May 2006. Two other institutions in Spain joined the prevalence study later to confirm the prevalence of grade 2 permanent alopecia. Grade 2 permanent alopecia was defined as complete alopecia that requires a wig after at least 18 months from the end of chemotherapy. Taking all 3 institutions together, the overall grade 2 PCIA occurred in 36 (10%) of 358 patients with Taxotere/docetaxel regimens reaching cumulative doses of ≥ 400 mg/m^2 but not in 59 patients receiving lower cumulative doses (300 mg/m^2) of Taxotere/docetaxel (e.g., dose response). The study also addressed the issue of whether regimens containing doxorubicin and cyclophosphamide (AC) or epirubicin and cyclophosphamide (EC) cause permanent alopecia in the absence of Taxotere/docetaxel. In the 306 patients receiving other chemotherapy regimens (including AC/EC regimens alone or followed by paclitaxel) there were no cases of grade 2 permanent alopecia. The study also looked at patients receiving endocrine therapy. There were no patients with grade 2 permanent alopecia who received endocrine therapy without chemotherapy. The incidence of Taxotere/docetaxel-induced grade 2 permanent alopecia was similar in patients with (22/221, 9.96%) and without endocrine therapy (14/137, 10.2%). The median follow-up of patients after the end of chemotherapy was 43 months (range 18-60 months).

---

[104] *Id.*

[105] *Id.*

[106] *Id.* at 3.

Kim (2017): This study was a cross-sectional survey retrospectively identifying early breast cancer patients who had received doxorubicin, cyclophosphamide alone or followed by a taxane as neoadjuvant or adjuvant chemotherapy and were at least 6 months after cessation of chemotherapy, with follow-up from completion of chemotherapy ranging from 6 months to 5 years. A questionnaire regarding alopecia as well as the measurement of hair density was conducted. Among the 265 patients who responded to the questionnaire, 19 (7.2%) reported severe alopecia (>50% of their scalp and lasting at least 6 months after the end of chemotherapy). Of those reporting severe alopecia, 2.7% had received doxorubicin and cyclophosphamide and 10.5% had also received a taxane. In the taxane regimens, 33.3% wore wig vs. 10.7% on non-taxane regimen. Table 1 from the paper notes that 122 of the 265 patients had chemotherapy-induced alopecia, and of this number 29 had not received a taxane-based regimen, and 93 had received a taxane-based regimen. Multivariate analysis showed only the chemotherapy regimen containing a taxane as an independent risk factor for pCIA (OR 4.75, with 95% CI 2.29 - 9.86, p<.001). There was no significant difference for endocrine treatment. Neither the publication, nor direct personal communication with the senior author revealed the attribution by specific taxane.[107]

Bourgeois (2010): A retrospective study, from May 2008 to May 2010, in which 108 cases of persistent alopecia or suboptimal hair regrowth after adjuvant chemotherapy were reported from 15 different institutions in OMIT (a network in France of the Drugs and Emerging Therapeutics Observatory). Of these 108 cases, 104 (96%) had received Taxotere/docetaxel – based treatment as adjuvant chemotherapy for their breast cancer. Of the 50 patients who answered a questionnaire, 38% to 45% complained of a moderate to severe alteration of the quality of their family and social lives. One year earlier (2009), Bourgeois had reported 61 of 63 cases after adjuvant chemotherapy with a Taxotere-containing regimen (fluorouracil + epirubicin + cyclophosphamide followed by Taxotere). In a presentation for the 37th Annual CTRC-AACR San Antonio Breast Cancer Symposium in 2014, Bourgeois provided an update on ERALOP, a retrospective study using a self-questionnaire targeting patients treated with FEC – Taxotere/docetaxel from 2008 to 2009 to estimate the incidence of persistent significant alopecia at 6 months after the last course of chemotherapy. 829 patients received a questionnaire and 653 (79%) responded. Six months after the last Taxotere/docetaxel course, persistent significant alopecia grade 2 was 8.6% (71 patients) and grade 1 was 32.6% (271 patients). At a median follow-up of 3.7 years, persistent significant alopecia grade 2 was 3.5% (29 patients) and grade 1 was 30% (248 patients).

---

[107] See footnotes 84 and 85, above.

Sedlacek (2006): A retrospective evaluation of consecutive treatment of 496 women with localized breast cancer. The patients were treated by Sedlacek from January 1994 through December of 2004 in a retrospective prospective controlled cohort study of consecutive patients. The chemotherapy regimens compared: Group A- 258 patients administered doxorubicin and cyclophosphamide regimens without taxanes (AC, FAC, A/CMF). Group B- 126 patients administered doxorubicin and cyclophosphamide plus paclitaxel/Taxol (AC/T, AT/T, AC/T dose dense, ATC, AC/Herceptin). Group C- 112 patients administered doxorubicin and cyclophosphamide plus docetaxel/Taxotere (AC/Tax, ATax, ACTax, AC/TaxXeloda, AC/Tax Herceptin, ATax/FAC, FAC/Tax). Women who underwent high-dose chemotherapy with stem cell rescue were excluded. Only patients with at least 1 year of follow-up post adjuvant chemotherapy were included. The average time from the last dose of chemotherapy was 48 months (range 19 to 85 months). Persistent significant alopecia, defined as <50% hair regrowth at least one year after chemotherapy, developed in 7/112 (6.3%) women with localized breast cancer treated with a Taxotere/docetaxel/doxorubicin/cyclophosphamide containing regimen. All were reported to be wearing wigs. No persistent significant alopecia occurred in those treated with a Taxol/paclitaxel/doxorubicin/cyclophosphamide -containing regimen, or in those treated with a doxorubicin/cyclophosphamide regimen without a taxane.

Crown (2017): Retrospective non-randomized cohort study of 300 patients with early stage breast cancer treated with adjuvant therapy with 3 different treatments. A telephone interview survey (approved by the Hospital audit committee) was conducted of early stage breast cancer patients recorded in their database (St. Vincent University Hospital, Dublin, Ireland) who had completed adjuvant or neo-adjuvant anthracycline and/or taxane-based chemotherapy on clinical trials more than 1 year earlier and assessed as to the number and severity of ongoing alopecia. Drug regimens were assessed with the following categories: Docetaxel regimen in 265 patients, anthracycline-non taxane regimen in 12 patients, and anthracycline + paclitaxel regimen in 23 patients. Alopecia persisting more than 1 year after the completion of chemotherapy was demonstrated in 40 patients in the docetaxel regimen, 1 patient in the anthracycline-non-taxane regimen, and 3 patients in the paclitaxel regimen. For the 191 patients receiving docetaxel and non-anthracycline regimen, there were 2 levels of cumulative exposure of the docetaxel. The alopecia was significantly increased e.g., dose response was demonstrated, with the higher cumulative dose of docetaxel i.e., at 300 mg/m2 (97 patients) the incidence was 7%, all grade 1, and at a dose of 450 mg/m2 (94 patients) it was 20% with a higher grade of alopecia (6% grade 2, 14% grade 1).

Thorp (2015): This retrospective study of prospectively evaluated patients (presented at the CTRC-AACR San Antonio Breast Cancer Symposium in 2014), used a questionnaire sent in October 2013 to 189 patients who had received docetaxel-based regimens for early stage breast

cancer in 2010 at their regional cancer center. The aim of the study was to determine the incidence, site, extent and duration of hair loss. Of the 189 questionnaires sent, 134 (71%) were returned. Of the respondents, 21 (15.8%) noted significant scalp hair loss, 13 (9.8%) gave equivocal responses, 99 (77.4%) had no significant scalp hair loss, and 1 patient did not answer the scalp hair loss question. 16 patients noted use of wigs and hair extensions. Lack of hair was also noted for a subset in other body areas, such as eyelashes and eyebrows. Long-term hair loss (up to 3.5 years after the last chemotherapy with a Taxotere/docetaxel regimen) occurs in 10 to 15% of patients, and from responses to the questionnaire questions, had a significant impact on the patients' quality of life. Univariate and multivariate analyses showed no significant association with other patient or treatment characteristics (e.g., endocrine treatment).

Freites-Martinez (2019): Eight-year retrospective, multicenter case study conducted between January 2009 and July 2017 in patients referred to the dermatology service from two comprehensive cancer centers and one tertiary-care hospital. The institutions included Memorial Sloan Kettering, New York, the Institut Universitair du Cancer, Toulouse, France and the dermatology service at University Federico II, Naples, Italy. Patients were eligible if they received only systemic cytotoxic chemotherapy with a clinical diagnosis of PCIA or received chemotherapy followed by endocrine therapies, but the alopecia was associated with endocrine therapy. Standardized photographs of the scalp, trichoscopy to assess hair diameter and hair density, and quality of life evaluations were conducted. Of 385 patients, 193 were excluded, and 192 included, including 98 with persistent alopecia attributed solely to chemotherapy, and 94 with alopecia attributed solely to endocrine therapy. Exclusions included 82 for chemotherapy-induced alopecia, 40 for other potential causes of alopecia (e.g., androgenetic, thyroid-related, telogen effluvium, targeted therapy, immunotherapy, and graft-vs-host disease) 35 for missing data, 19 with previous scalp radiotherapy, and 17 for having a combined attribution of alopecia from cytotoxic chemotherapy and endocrine therapy. 79 (81%) of the 98 patients with PCIA had a diagnosis of breast cancer, and 89 (95%) of the 94 with alopecia attributed to endocrine therapy had a diagnosis of breast cancer. The most common agent associated with PCIA was taxane-based chemotherapy (80 patients with 47 on paclitaxel, 31 on docetaxel, and 2 with both), and grade 2 alopecia was seen in 29 of 75 patients. It was not clear from the methods section how the 385 patients were identified, nor the methodology for excluding more than half of the patients. In addition, the loss to follow-up on the subset of 98 patients with PCIA was not explained. Of the 98 in the PCIA category, only 75 of the 98 had clinical characteristics of their alopecia noted, only 45 of the 98 had trichoscopy performed, and only 41 of the 98 had data on quality of life; it was not clear how many in the subset of 75 or 45 or 41 patients had a diagnosis of breast cancer, and the specific regimen used.

Kluger (2012): This retrospective study analyzed the clinical and histological features of severe permanent alopecia that was diagnosed between 2007 and 2011 in 20 breast cancer patients receiving treatment of fluorouracil + epirubicin + cyclophosphamide followed by Taxotere/docetaxel. One of the 20 had also received Taxol/paclitaxel, in addition to Taxotere/docetaxel. Permanent alopecia was defined as absent or incomplete hair regrowth at ≥ 6 months post-chemotherapy. Health-related quality of life (QoL) was assessed by a self-administered questionnaire, the Dermatology Life Quality Index (DLQI) and by whether or not the patient permanently wore a medical hair prosthesis (wig). The DLQI is a validated, rapid and highly sensitive test used in routine clinical practice to evaluate the QoL for various skin diseases, and evaluates 10 items, with higher scores indicating greater impairment of QoL. The mean DLQI in 18 patients administered the test was 8.66, compared to a mean of 0.5 in a healthy population. Severe impairment was reported by 7 of the 18 patients (38%, score 11-20). 70% (14/20) wore a hair prosthesis (i.e., a wig) or scarf (1 patient).

Fonia (2017): This retrospective study incorporated data from April 2010 through August 2013 and identified 10 breast cancer patients treated with Taxotere/docetaxel-based regimens (1 also received paclitaxel in addition to Taxotere/docetaxel) who developed permanent alopecia lasting more than 6 months after the end of chemotherapy. The follow-up was more than 18 months post-chemotherapy in all patients. Of the 10 patients with PCIA, all received docetaxel regimens - 5 had no endocrine therapy, 7 had no anthracycline, and 4 had neither an anthracycline or cyclophosphamide. One had received 3 cycles of docetaxel and 1 cycle of paclitaxel. All 10 patients had alopecia of the scalp, and 3/10 also had hair loss of eyebrows and eyelashes and 5/10 had loss of body hair. All patients had diffuse hair loss on their scalp with residual sparse hair. After the end of chemotherapy, hair regrowth was partial in 9 of 10 patients, with minimal regrowth in 1 patient. The patient wore a wig and had slow but complete hair regrowth within 6 months after starting treatment with topical minoxidil.

Miteva (2011): Describes a retrospective clinicopathological study of 10 cases of permanent alopecia after systemic chemotherapy, in which 6 cases were breast cancer patients treated with Taxotere/docetaxel. The histologic findings of permanent alopecia after chemotherapy were those of a nonscarring alopecia. The cases came from patients who were referred for treatment of hair loss to the Department of Dermatology (9 cases in Bologna, Italy and 1 case in Miami, Florida). All were evaluated at least 12 to 24 months after the end of chemotherapy. The severity of hair loss ranged from very severe to severe, and all women patients wore a wig.

Tallon (2010): This case report was of a woman with breast cancer, negative for ER and PR and on no endocrine therapy and no anthracycline, presenting with persisting alopecia 13 months after completion of adjuvant chemotherapy with a Taxotere/docetaxel-containing regimen. She had no prior history of hair loss and had no pre-existing hair loss. Two weeks after the start of

Exhibit J

EXPERT REPORT OF

Laura M. Plunkett, Ph.D., DABT

October 21, 2019

I. Training and Qualifications

1. I am a pharmacologist, toxicologist, United States Food and Drug Administration (FDA) regulatory specialist and principal of a consulting company known as Integrative Biostrategies, LLC. Integrative Biostrategies, based in Houston, Texas, is a consulting firm that works at the interface of biological science, regulatory affairs and business decisions to provide its clients with science-based solutions to issues associated with product development and stewardship. Before joining Integrative Biostrategies in 2001, I was head of the consulting firm known as Plunkett & Associates.

2. I am board-certified as a Diplomate of the American Board of Toxicology. I am a member of several professional organizations and have authored or co-authored numerous scientific publications. I have over twenty years of experience in the areas of pharmacology and toxicology and have worked in both government and academic research. I have taught pharmacology and toxicology at the undergraduate and postgraduate levels.

3. I received a B.S. degree in 1980 from the University of Georgia and a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy in 1984. My doctoral research was focused in the area of cardiovascular pharmacology and specifically dealt with delineating neurochemical mechanisms responsible for the cardiac toxicity of digitalis glycosides.

4. From June 1984 through August 1986, I was a Pharmacology Research Associate Training (PRAT) fellow at the National Institute of General Medical Sciences, Bethesda, Maryland. I worked in a neurosciences laboratory of the National Institute of Mental Health. My research focused on the role of various brain neurochemical systems involved in the control of autonomic nervous system and cardiovascular function.

referred to as "anagen effluvium", which is the sudden, diffuse loss of anagen-phase, or growth-phase hair, that occurs within days to weeks of exposure to an anti-neoplastic drug. Anagen effluvium is more common and severe when there is a combination of anti-neoplastic agents employed. This is the concept of additivity in pharmacology and toxicology (Eaton and Gilbert, 2013), which occurs when more than one drug or chemical that have common toxic effects are given together.

32. Both docetaxel and paclitaxel use are known to cause reversible alopecia in patients (see FDA labeling for Taxotere and Taxol). The toxic effect of drugs like docetaxel that lead to hair loss include complete arrest of hair formation by direct toxic insult to the rapidly dividing cells in the hair follicle (Trueb, 2009). Such alopecia typically is seen within two to four weeks after treatment begins and hair regrowth is usually seen within six months of treatment ending (Tallon *et al.* 2010). Thus, in most cases, when drug therapy is completed, the drug is eliminated from the body and the hair will regrow. The lack of regrowth once drug exposure has ceased is what distinguishes permanent, irreversible alopecia, which is recognized in the medical literature as hair that fails to regrow or substantially regrow at least by six months after treatment has ended (Tallon *et al.* 2010; Namini *et al*. 2016; Kim *et al.* 2017; Kang *et al.* 2018). Although the general definition of hair loss still seen at six months after ending treatment is used in many studies, clinical evidence indicates that the lack of regrowth has been reported to persist for years (discussed below in more detail). Thus, the injury is not simply loss of hair but is failure of hair to regrow after drug exposure has ceased.

33. Although many anti-neoplastic drugs are associated with reversible hair loss during treatment, there is a difference in the propensity for the permanent, irreversible hair loss that has been linked to Taxotere use as compared to many other drugs. Reviews of the issue of irreversible alopecia generally describe it as a "rare" event with chemotherapy (Tallon *et al.* 2010). A review of the available data indicate that Taxotere has been associated with irreversible hair loss to a greater extent than other chemotherapeutic drugs, including Taxol (discussed below in more detail). In fact, the evidence linking Taxotere exposure with permanent, irreversible hair loss includes controlled clinical trial data as well as epidemiological data (case series) and

individual case reports. When the available evidence is considered, the weight-of-the-evidence indicates it is biologically plausible that Taxotere can cause CIPAL/ PCIA.

34. The first report of docetaxel-induced irreversible hair loss appeared in the scientific literature in 2001 (Nabholtz *et al.* 2001. *J. Clin. Oncol.* 19:314-321) and related to results from an investigator that was participating in a Taxotere clinical trial. Patients had been enrolled in a Phase II clinical study and the authors reported that the *"most common treatment-related chronic nonhematologic toxicity was alopecia (87%) with long-lasting (longer than 2 years) partial alopecia in four* patients*"* (see Nabholtz paper page 318; Sanofi_00217670). The percentage of patients at two years with irreversible alopecia was 4/54 or 7.4%; such a rate of occurrence would be considered common (frequent) based on definitions provided by the World Health Organization (WHO) for pharmacovigilance practices; WHO defines "very common" as a rate > 1 in 10, "common" (frequent) as a rate > 1 in 1000 but < 1 in 10, "uncommon" (infrequent) as a rate > 1 in 1000 but < 1 in 100, "rare" as a rate > 1 in 10,000 and < 1 in 1000, and "very rare" as a rate < 1 in 10,000[5]. Given that Dr. Nabholtz was an investigator for Sanofi (see page 331 of Gustavson deposition), this paper was of particular importance.

35. In 2006, a presentation at the San Antonio Breast Cancer Symposium by Dr. S.M. Sedlacek (Sedlacek, 2006) described clinical experience in treating breast cancer based on a retrospective review of patient data in his clinical practice. His report would be considered a type of epidemiological investigation. He reported that alopecia associated with docetaxel therapy as an adjuvant to doxorubicin/cyclophosphamide chemotherapy was irreversible in some patients (he called the condition "persistent significant alopecia" and abbreviated it as "PSA"). PSA rates reported for the three different treatment groups in his study were 6.3% in women administered doxorubicin plus Taxotere, 0% in women administered doxorubicin plus Taxol, and 0% in women administered doxorubicin without a taxane. Again, the rate of irreversible alopecia (PSA) reported by this physician would be considered a common adverse event in the Taxotere-treated group (consistent with WHO definitions). The rate of occurrence of irreversible alopecia in Taxotere-treated patients in this clinical population was higher as compared to Taxol and was not a rare event. The comparison of Taxotere experience with and without doxorubicin allows for

[5] see http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf

consideration of the contribution of each drug independently to the risk in the patients. Taxotere use was associated with an increased risk of permanent, irreversible alopecia, a risk that was not seen with use of doxorubicin alone or with doxorubicin combined with Taxol use. Therefore, Taxotere carried an independent risk of CIPAL/ PCIA and was a substantial contributing factor to the condition in the women studied.

36. In 2009, Prevezas and colleagues described clinical experience in their dermatological practice with two patients that developed *"irreversible and severe alopecia";* one woman had received Taxotere and letrazole, while the other woman had received Taxol only. The authors concluded with respect to the woman who had received Taxotere: *"We think that the irreversibility can be attributed only to the cytotoxic effect of docetaxel [Taxotere]."* These case reports of permanent, irreversible alopecia added to the evidence that began to accumulate starting in 2001.

37. Also, in 2009, a presentation was made at the San Antonio Breast Cancer Symposium by Dr. Hugues Bourgeois[6]. Dr. Bourgeois summarized data collected from 15 private institutions and public hospitals in France and reported that adjuvant chemotherapy[7] can lead to persistent alopecia or suboptimal hair regrowth in patients. The investigators based their findings on case report forms for 82 patients (median age, 60 years) who received adjuvant treatment for breast cancer and were completed by physicians between May 2008 and October 2009 (also a type of epidemiological investigation). Irreversible alopecia was reported in all of the women. Dr. Bourgeois stated that he felt the 100 mg/m^2 dosage of Taxotere was *"too high"* as a recommended dosage and that he gives *"them [his patients] the choice [of] 4 courses of Taxotere with a [small percent chance] of permanent hair loss, or 12 weeks of Taxol with no risk of permanent hair loss. For the efficacy, it is the same."*

38. In each of these papers and presentations reported through 2009, the authors were describing a new finding of irreversible or irreversible alopecia, that was different than the chemotherapy-induced alopecia that typically had been associated with taxanes previously, and

[6] http://www.mdmag.com/journals/obtn/2010/march2010/sabcs_interview_series
[7] Adjuvant chemotherapy is defined as additional cancer treatment after the primary treatment has been completed that is given to decrease the risk of cancer reoccurrence.

also appeared to be more common in Taxotere-treated patients. The authors attributed use of Taxotere to a type of hair loss that was different than the drug-induced alopecia that is linked to most chemotherapy drugs. When considered together, these papers provide evidence that it is biologically plausible that Taxotere can cause CIPAL/PCIA as well as providing evidence that CIPAL/ PCIA in patients receiving Taxotere is not rare.

39. In 2010, a literature review on chemotherapy-induced irreversible alopecia was published (Tallon *et al.* 2010). The authors also described a case of irreversible hair loss in a woman following standard dose chemotherapy with docetaxel, carboplatin and trastuzumab for breast cancer. The authors suggested that docetaxel was the causative agent in their patient. Important conclusions reached by the authors included the following:

- Chemotherapy-induced hair loss is typically considered completely reversible, but this is not always the case.
- Physicians and patients need to be aware of the rare possibility that alopecia following chemotherapy can be persistent.

40. In response to the publication by Tallon *et al*. (2010), a *"Letter to the Editor"* was published regarding this paper in 2013 (Tosti *et al.* 2013). Tosti and colleagues reported that five additional patients on docetaxel therapy had irreversible alopecia (Tosti *et al*. 2013). In their letter, the physicians stated: *"The real prevalence of this devastating long-term side effect of docetaxel is unknown, and efforts should be made to understand the mechanism of follicle destruction and to identify strategies for possible prevention."* Yet, clinical data from docetaxel trials (Nabholtz *et al.* 2001; Sedlacek, 2006) had determined that irreversible alopecia was not a rare event in their clinical populations, a finding that is supported by the results of another Taxotere clinical trial known as TAX316 (discussed in detail below) where again the rate of CIPAL/ PCIA was not rare.

41. Two additional papers appeared in the scientific literature in 2011 describing docetaxel or paclitaxel use and irreversible alopecia (Miteva *et al.* 2011; Palamaras *et al.* 2011). Miteva and colleagues reported on ten cases of irreversible alopecia, six of whom had been treated with docetaxel (Miteva *et al.* 2011); the other patients in the case series included three

patients treated with busulfan for acute myelogenous leukemia, and one patient treated with cisplatin and etoposide for lung cancer. Notably, none of the women had a history of hair loss before chemotherapy treatment, and their hematological and endocrine assessment were all within normal ranges. The authors stated: *"Permanent alopecia after chemotherapy is unique for 2 reasons: (1) it is not reversible and (2) it is not cicatricial. In fact, the pathology shows lack of fibrosis and a preserved number of follicular units. This makes this condition very difficult to recognize under the microscope. It is likely that most pathologists would sign such cases as AGA if not provided with the clinical information." [see page 350 of Miteva et al. 2011]* In the second paper, Palamaras and colleagues described a retrospective chart study of patients who had attended their dermatology practice for treatment of hair loss during the previous seven years. They compared their findings with reports identified by a literature search. Of the seven patients they found in their practice with persistent or irreversible alopecia, five were women that had been exposed to docetaxel (Taxotere) as part of a chemotherapeutic regimen while two other women had been exposed to busulphan. The authors also reported that on histopathologic examination, the patients scalp tissue showed "a marked reduction of follicular units with an increase in vellus hair formation and absence of any significant inflammation or scarring", findings they stated were similar to those of Prevezas and colleagues where patients had been treated with taxanes.

42. In 2012, docetaxel-associated irreversible alopecia again was reported in patients being treated for breast cancer with taxanes (Bourgeois *et al.* 2012; Kluger *et al.* 2012). The publication by Bourgeois and colleagues is an abstract from the 35th annual meeting of the San Antonio Breast Cancer Symposium (2012) where the authors reported on cases of irreversible alopecia in a French database (ALOPERS). The database contained more than 100 patients with persisting alopecia and the authors stated that docetaxel was the drug linked with the adverse event in a majority of the patients. The authors concluded that docetaxel 75–100 mg/m^2 was the common agent in the majority of patients and that 43% of patients lacked hair regrowth more than 24 months after their last chemotherapy infusion. They also concluded: *"Optimal information of patients about alopecia and persisting alopecia appears to be mandatory before treatment: 47% of patients undergo a psychological shock during hair loss."* They pointed to the results of a Taxotere clinical trial finding to support their conclusions. They stated: *"Moreover,*

Exhibit K

Docetaxel and Irreversible Alopecia

David Madigan, PhD

1. Background

1. I am Professor of Statistics, former chair of Statistics, and former Executive Vice-President of Arts and Sciences and Dean of the Faculty of Arts and Sciences at Columbia University in New York City. I was chair of the Columbia Department of Statistics from 2008 to 2013. I served as EVP and Dean from 2013 to 2018. I received my bachelor's degree in Mathematical Sciences from Trinity College Dublin in 1984 and was awarded the College's gold medal. In 1990, I received a Ph.D. in Statistics, also from Trinity College. I have worked in the past for KPMG, SkillSoft, University of Washington, AT&T Labs, and Soliloquy Inc. From 2005 to 2007 I was Professor of Statistics and Dean of Physical and Mathematical Sciences at Rutgers University. Prior to serving as Dean I was Director of the Rutgers University Institute of Biostatistics. I am an elected Fellow of both the Institute of Mathematical Statistics and the American Statistical Association, as well as the American Association for the Advancement of Science, and was the 36th most cited mathematician worldwide from 1995-2005. I was an Institute of Mathematical Statistics Medallion Lecturer in 2009. I served a term as the Editor of *Statistical Science* from 2008 to 2010, the highest impact journal in Statistics.

2. I have published more than 180 technical papers on Bayesian statistics, biostatistics, pharmacovigilance, statistical graphics, Monte Carlo methods, computer-assisted learning, information retrieval, and text mining. Within the last few years I have consulted for Clarus Therapeutics, Jarvik Heart, Lilly, Merck, Novartis, and Pfizer on a variety of issues, many related to drug safety. In the past, I advised Boehringer Ingelheim on issues related to pharmacovigilance. I have considerable statistical experience with clinical trials including the design and analysis of pain studies at the University of Washington and the Fred Hutchinson Cancer Research Center, and more generally as a statistical consultant to multiple internal and external clients, particularly while I was director of the Institute of Biostatistics at Rutgers University, and continuing with Shire and Bayer.

3. Drug safety is one of my significant research interests, with a focus on the development and application of statistical methods for pharmacovigilance. I have published my work in *Drug Safety*, *Pharmacoepidemiology and Drug Safety*, *Therapeutic Advances in Drug Safety*, *Epidemiology*, the *American Journal of Epidemiology*, and other journals. I have also served as an investigator in the Mini-Sentinel project. Mini-Sentinel is a pilot project sponsored by the FDA to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. In 2010-11, I led the Mini-Sentinel Working Group on case-based methods in active surveillance. In addition, from 2010 to 2013 I was a Principal Investigator for the Observational Medical Outcomes Partnership (OMOP), a public-private partnership between the FDA and the pharmaceutical industry. The partnership conducted a multi-year initiative to research methods that are feasible and useful to analyze existing

5. Analysis of Internal Safety Databases

49. I conducted an analysis of Sanofi's global pharamacovigilance database to identify reports of irreversible alopecia. The manufacturer conducted similar analyses that I discuss below. To identify reports of irreversible alopecia, Dr. Antonella Tosti, Professor of Dermatology and Cutaneous Surgery at the University of Miami Miller School of Medicine, provided the following list of search terms:

- permanent
- irreversible
- bald
- baldness
- chronic
- persistent
- hair never grew back
- still have no hair
- no hair regrowth
- hair not regrowing
- hair has not returned
- alopecia ongoing

Drs. Feigal and Plunkett confirmed this selection of terms. I added linguistic variations to these search terms (also confirmed by Dr. Tosti) - I provide my perl code in Appendix 5.

50. My analysis yields 311 reports. The second column of Table 6 below shows the accumulation by year. The third column excludes reports with either an outcome of "recovered" or an end date. The rightmost column shows the number of irreversible reports as a percetange of all alopecia reports.

Table 6. Cumulative reports of irreversible alopecia in Sanofi's global pharmacovigilance database

Year	Cumulative Number of Reports	Cumulative Number of Reports Excluding "Recovered"	Number of Reports Excluding "Recovered" as % of Total Alopecia Reports
1999	6	6	14.3%
2001	7	7	0.2%
2002	8	8	0.3%
2003	14	12	5.7%
2004	22	20	8.5%
2005	30	28	20.5%
2006	37	34	6.3%

2007	42	39	8.3%
2008	50	47	11.6%
2009	84	78	40.3%
2010	176	156	52.3%
2011	197	175	16.4%
2012	227	203	26.2%
2013	267	241	31.7%
2014	291	264	23.5%
2015	311	282	22.5%

51. On 18 January 2011 Sanofi conducted an analysis of irreversible alopecia in their global pharamacovigilance database through 9 December 2010.[47] Dr. Emanuel Palatinsky authored the report. Alopecia events were identified by the MedDRA Higher Level Term "alopecias." The search identified 142 reports of irreversible alopecia defined as not recovered 12 or more months after the last dose of chemotherapy. The analysis excluded reports with an unknown outcome and reports where the latest outcome was reported less than 12 months following the last dose of chemotherapy. The report concluded that these 142 reports "revealed no evidence of a causal relationship" between docetaxel and irreversible alopecia.

52. On 11 November 2015 the manufacturer conducted another analysis of the global pharamacovigilance database, this one authored by Dr. Nanae Hangai. Specifically, Sanofi performed a cumulative search to 7 October 2015 for alopecia reports.[48] Alopecia events were identified by the MedDRA Higher Level Term "alopecias." The search identified 117 reports of irreversible alopecia defined as having either "permanent" or "irreversible" mentioned in the verbatim section of the report, or, alopecia that lasted more than 2 years with an outcome of not recovered, recovering, or unknown.

53. On the basis of the totality of the evidence available to it, Sanofi concluded that the "cumulative weighted evidence is sufficient to support a causal association between docetaxel and permanent/irreversible alopecia." The information available to Sanofi at this time was not appreciably different from what was available at the time of the 2011 report. In fact, that report used a different definition of irreversible alopecia that yielded a *larger* number of cases. My own analysis in Table 4 using Dr. Tosti's definition shows that the number of reports of irreversible alopecia surpassed 117 sometime in 2010.

54. I note that it is not possible to directly calculate the rate at which irreversible alopecia occurs in the population (either per person or per person-time) from spontaneously reported events such as those in Sanofi's database. The FDA's 2005 Guidance for

[47] Sanofi_04353204/Sanofi_04353204
[48] Sanofi_00829788

Industry on "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment" states:

> "In pharmacoepidemiologic studies (see section V.A), the numerator (number of new cases) and denominator (number of exposed patients and time of exposure or, if known, time at risk) may be readily ascertainable. In contrast, for spontaneously reported events, it is not possible to identify all cases because of under-reporting, and the size of the population at risk is at best an estimate."

Spontaneously reported events do permit calculation of reporting rates (as utilized in my FAERS analysis above) but the FDA goes on to state:

> "Reporting rates can by no means be considered incidence rates, for either absolute or comparative purposes."

6. Irreversible Alopecia in Observational studies

55. My searches yielded four studies:

Crown, J., Walshe, J., Fennelly, D., Long, J.C., Cairney, S., McDonnell, D., Ballot, J., Wildes, D., Sills, E. and Gullo, G. (2017). Incidence of permanent alopecia following adjuvant chemotherapy in women with early stage breast cancer. *Annals of Oncology*, *28*(suppl_5).

Kang, D., Kim, I.R., Choi, E.K., Im, Y.H., Park, Y.H., Ahn, J.S., Lee, J.E., Nam, S.J., Lee, H.K., Park, J.H. and Lee, D.Y. (2019). Permanent Chemotherapy-Induced Alopecia in Patients with Breast Cancer: A 3-Year Prospective Cohort Study. *The Oncologist*, *24*(3), pp.414-420.

Martín, M., de la Torre-Montero, J.C., López-Tarruella, S., Pinilla, K., Casado, A., Fernandez, S., Jerez, Y., Puente, J., Palomero, I., del Val, R.G. and del Monte-Millan, M. (2018). Persistent major alopecia following adjuvant docetaxel for breast cancer: incidence, characteristics, and prevention with scalp cooling. *Breast Cancer Research and Treatment*, *171*(3), pp.627-634 (and correction pp.635-636)

Sedlacek, S. (2006). Persistent significant alopecia (PSA) from adjuvant docetaxel after doxorubicin/cyclophosphamide (AC) chemotherapy in women with breast cancer. *Breast Cancer Research and Treatment*, *100*.

56. Table 7 below summarizes the findings.

Table 7. Reports of irreversible alopecia in observational studies

Study	**Docetaxel**	**Non-Docetaxel**	**Odds Ratio**	**Fisher Exact Test**	**Endpoint**
Crown	39/260	4/35	1.37	p = 0.80	Severe/total ongoing alopecia @ greater than 1 year

Kang	See text below		8.01	n/a	Permanent chemotherapy-induced alopecia @ 3 years
Martín[49]	98/417	24/306	3.61	$p = 1.2 \times 10^{-8}$	Persistent alopecia @ 1.5 to 5 years
Sedlacek	7/112	0/384	54.7	$p = 2.6 \times 10^{-5}$	Persistent significant alopecia @ greater than 1 year

57. Kang et al. do not provide raw counts by regimen but, comparing docetaxel to non-docetaxel regiments, they report an odds ratio of 8.01 (95% confidence interval 1.20-53.26). Their analysis adjusted for age, hair density, and thickness at diagnosis.

58. A random effects meta analysis of these four studies yields an odds ratio of 4.13, 95% confidence interval (1.44 , 11.81), p=0.008. I note that there is some between-study heterogeneity, I^2=62.9%, albeit not statistically significant (Q=7.10, p=0.07). Appendix 6 provides the R code.

7. Irreversible Alopecia in the TAX 301 and TAX 316 studies

59. TAX 316 was a phase 3 controlled trial that randomized patients with high-risk operable breast cancer with negative axillary lymph nodes to either docetaxel (TAC) or 5-fluorouracil (FAC), both provided in combination with doxorubicin and cyclophoasphamide. The study began in 1997 and the last patient visit occurred in Janaury 2010. Study treatment comprised six 3-week cycles. Follow-up visits were to be every 12 weeks for the first two years, every six months for years 3 to 5, and then annually for 10 years.

60. TAX 301 was a similar phase 3 controlled trial that also randomized patients with high-risk operable breast cancer with negative axillary lymph nodes to either docetaxel (TAC) or 5-fluorouracil (FAC), both provided in combination with doxorubicin and cyclophoasphamide. The study began in 1999. Study treatment comprised six 3-week cycles. Follow-up visits were to be every 12 weeks for the first two years, every six months for years 3 to 5, and then annually for 10 years.

61. The majority of patients in TAX 316 experienced alopecia while on treatment (98% of TAC patients and 97% of FAC patients). At study completion, 29 of 744 TAC patients had ongoing alopecia as compared with 16 of 738 FAC patients (risk ratio 1.79, 95% confidence interval (0.98 , 3.27)). Of note, for 661 TAC patients and 629 FAC patients, resolution of alopecia is explicitly noted in the clinical trial data. Figure 4 below shows the follow-up times for the patients with ongpoing alopecia at study completion.

[49] Personal communication, 20th September 2019.

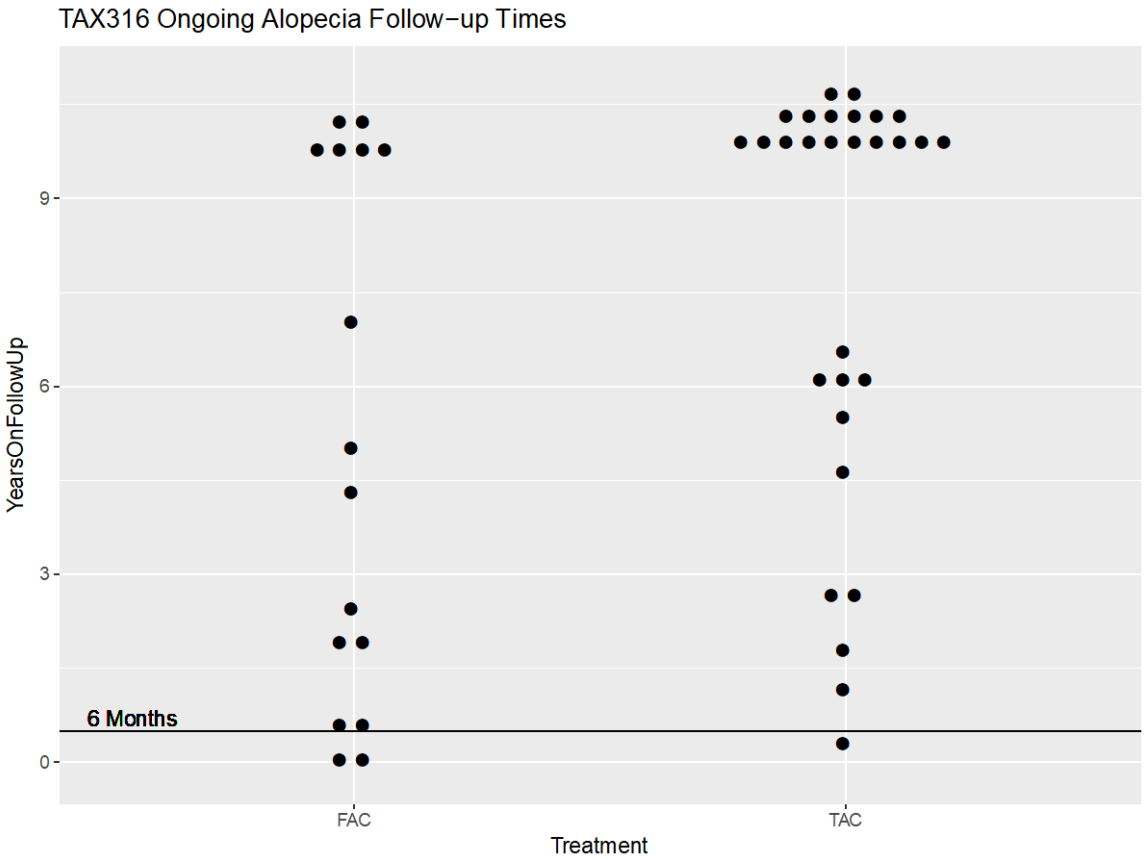


Figure 4. Follow up times for the 45 patients with ongoing alopecia at the completion of TAX316

62. The majority of patients in TAX 301 also experienced alopecia while on treatment (97% of TAC patients and 98% of FAC patients). Unfortunately, the trial data fail to explicitly capture either the continuation of alopecia into the follow-up phase or alopecia resolution for the majority of patients. Only 49 of the 531 TAC and 35 of the 520 FAC patients were noted as having alopecia in follow-up. Of the 49, 3 were unresolved at study completion as compared with 1 unresolved in the FAC group. Given that the patients enrolled in TAX 316 and TAX 301 were very similar, I know of no reason for this striking asymmetry between the two studies. All but 9 of the 531 TAC patients had at least one year of follow-up but inexplicably, alopecia status, whether resolved or not, failed to be recorded for the majority of patients. I note that the 49 TAC patients with alopecia recorded in follow-up were concentrated in just 12 of the 55 study sites; phrased differently, 43 of the 55 study sites failed to record a single patient with alopecia in follow-up. More than half of the 49 patients (26) were in two particular sites with site-specific follow-up alopecia rates exceeding 80%

63. Follow-up in TAX 301 for non-alopecia adverse events also seems to be poor: 137 of 1,051 patients in 301 have non-alopecia AEs in followup as compared with 1,267 of 1,480 patients in 316.

64. I also considered the elapsed time between the end of treatment (plus 30 days) and any alopecia resolution. Table 8 below shows the results.[50]

Table 8. Numbers of patients with resolution of alopecia within different periods of time from the beginning of follow-up.

TAX 316				
Not resolved within:	TAC (*n*=744)	FAC (*n*=736)	Rate Ratio	p-value
22 weeks	178	141	1.25	0.026
6 months	112	82	1.35	0.026
12 months	53	27	1.94	0.003
24 months	36	19	1.87	0.022
60 months	31	16	1.92	0.029
120 months	29	16	1.79	0.053
TAX 301				
Not resolved within:	TAC (*n*=531)	FAC (*n*=520)	Rate Ratio	p-value
22 weeks	11	2	5.39	0.013
6 months	9	1	8.81	0.012
12 months	4	1	3.92	0.186
24 months	3	1	2.94	0.327
60 months	3	1	2.94	0.327
120 months	3	1	2.94	0.327

65. Following the interim analysis, Sanofi produced a series of Safety Update Reports (SURs) for TAX 316 and Table 9 shows the irreversible alopecia finding as of the dates of these reports. Equivalent reports for TAX 301 appear no to be available but had already reached 3-versus-1 by the cutoff date of the TAX 301 interim analysis.

[50] This analysis uses SAS data files from SA-VOL-170. I note the the same analysis using the SAS files from SA-VOL-208 yields slightly different but qualitatively indistinguishable results.

Table 9. Numbers of patients with resolution of alopecia as presented in successive Safety Update Reports.

TAX 316				
Report Year:	TAC (*n*=744)	FAC (*n*=736)	Rate Ratio	p-value
2004 (interim)	22	9	2.42	0.020
2005	21	8	2.60	0.016
2006	21	8	2.60	0.016
2007	21	8	2.60	0.016
2008	21	8	2.60	0.016
2009	21	8	2.60	0.016
Random Effects Meta-Analysis				
Report Year:	TAC	FAC	Rate Ratio	p-value
2004 (interim)	25	10	2.47	0.015
2005	24	9	2.63	0.013
2006	24	9	2.63	0.013
2007	24	9	2.63	0.013
2008	24	9	2.63	0.013
2009	24	9	2.63	0.013

66. A random effects meta-analysis combining the data from the two studies at completion yields a rate ratio of 1.85 with a corresponding 95% confidence interval (1.04 , 3.31) and a p-value of 0.04. Fixed effects meta-analysis, both classical and exact, and pooled analysis yield similar findings. Appendix 7 provides the R code.

8. Summary

67. Based on my education, training and experience, and the data analyzed herein, including the identification of safety signals in FAERS in the 2000's, my analyses of Sanofi's internal pharmacovigilance database, my review of observational studies, and the results from Sanofi's TAX 316 and TAX 301clinical trials, there is adequate statistical evidence that Taxotere (docetaxel) causes permanent/ irreversible alopecia. This statistical evidence was available to Sanofi years before Sanofi reached its conclusion in 2015 that there is a causal association between Taxotere (docetaxel) and permanent/ irreversible alopecia.

David Madigan, PhD
October 20th, 2019